47

=> d his 1

(FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 14:22:24 ON 28 AUG 2003)
L25 67 DUP REM L24 (76 DUPLICATES REMOVED)

=> d que l25
L3 34 SEA CAPELLO M?/AU
L4 12 SEA CHADDERDON R?/AU
L5 5877 SEA HARRISON L?/AU
L6 76 SEA DELVALLE A?/AU
L7 126 SEA DEL VALLE A?/AU
L8 6110 SEA (L3 OR L4 OR L5 OR L6 OR L7)
L9 36 SEA HOOKWORM AND L8
L10 12831 SEA HOOKWORM OR ANCYLOSTOMA OR NECATOR
L11 1142 SEA A(A)(DUODENALE OR CEYLANICUM OR CANINUM)
L12 476 SEA N(A) AMERICANUS
L13 13108 SEA (L10 OR L11 OR L12)
L14 78 SEA L13 AND PLATELET#
L15 86 SEA L13 AND INTEGRIN?
L16 20 SEA L13 AND (GPI? OR GP1?)
L17 170 SEA L9 OR (L14 OR L15 OR L16)
L18 75 SEA L17 AND (RECOMBINAN? OR VARIAN? OR MUTAN? OR HOMOLOG? OR FRAGMENT?)
L19 125 SEA L17 AND INHIBIT?
L20 133 SEA L18 OR L19
L21 15 SEA L17 AND (EPINEPHRINE# OR THROMBIN? OR ADP)
L22 137 SEA L20 OR L21
L23 23 SEA L17 AND (VACCIN? OR IMMUNIS? OR IMMUNIZ?)
L24 143 SEA L22 OR L23
L25 67 DUP REM L24 (76 DUPLICATES REMOVED)

=> d ibib abs l25 1-67

L25 ANSWER 1 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2003315295 MEDLINE
DOCUMENT NUMBER: 22728150 PubMed ID: 12805489
TITLE: UK-279,276, a neutrophil **inhibitory** glycoprotein, in acute stroke: tolerability and pharmacokinetics.
AUTHOR: Lees Kennedy R; Diener Hans-Christoph; Asplund Kjell; Krams Michael
CORPORATE SOURCE: University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT, UK. (UK-279,276-301 Study Investigators).
k.r.lees@clinmed.gla.ac.uk
SOURCE: STROKE, (2003 Jul) 34 (7) 1704-9.
Journal code: 0235266. ISSN: 1524-4628.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030708
Last Updated on STN: 20030802
Entered Medline: 20030801

Search completed by David Schreiber 308-4292

AB BACKGROUND AND PURPOSE: UK-279,276, a **recombinant** glycoprotein, binds selectively to the CD11b/CD18 **integrin** on neutrophils and has the potential to modulate the neuroinflammation associated with acute stroke. After preclinical evidence of neuroprotection, UK-279,276 has entered clinical development. The purposes of this study were to evaluate the safety and tolerability of UK-279,276 and to examine its pharmacokinetics and pharmacodynamics (binding to neutrophil CD11b) in patients with acute stroke. METHODS: This was a multicenter, double-blind, dose-escalation study in 176 patients randomized to a single intravenous dose of UK-279,276 (6 cohorts: 0.06, 0.1, 0.2, 0.5, 1.0, 1.5 mg/kg) or placebo (3:1 randomization within each cohort) within 12 hours of stroke onset. RESULTS: Age and stroke severity were well balanced across groups, with a mean age of 70 years (range, 39 to 92 years) and moderate baseline stroke severity (mean Scandinavian Stroke Scale score, 36.5 to 43.2; mean National Institutes of Health Stroke Scale score, 6.3 to 8.5). UK-279,276 was well tolerated at doses up to 1.5 mg/kg. There was no evidence of a relationship between dose of UK-279,276 and adverse events or clinical chemistry or hematology laboratory tests, or of an increased incidence of infection-related adverse events with the study drug. A dose-dependent UK-279,276-specific IgG antibody response was observed in patients treated with the 1.0- and 1.5-mg/kg doses. UK-279,276 displayed nonlinear pharmacokinetics across the dose range investigated. The duration of CD11b saturation was dose dependent, with >80% saturation achieved for at least 7 days after treatment with UK-279,276 1.0 and 1.5 mg/kg. CONCLUSIONS: UK-279,276 was well tolerated in acute stroke patients at single doses up to 1.5 mg/kg. Further clinical investigation of UK-279,276 is ongoing.

L25 ANSWER 2 OF 67 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003321665 IN-PROCESS
DOCUMENT NUMBER: 22735468 PubMed ID: 12850261
TITLE: Isolation and molecular cloning of a secreted **hookworm platelet inhibitor** from adult **Ancylostoma** caninum.
AUTHOR: **Del Valle Antonio**; Jones Brian F; **Harrison Lisa M**; **Chadderdon Robert C**; Cappello Michael
CORPORATE SOURCE: Department of Pediatrics, Yale University School of Medicine, 464 Congress Avenue, New Haven, CT 06520-8081, USA.
CONTRACT NUMBER: HD007388 (NICHD)
SOURCE: MOLECULAR AND BIOCHEMICAL PARASITOLOGY, (2003 Jul) 129 (2) 167-77.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030710
Last Updated on STN: 20030802

AB Hookworms, bloodfeeding intestinal nematodes, are a leading cause of iron deficiency anemia in the developing world. These parasites have evolved potent mechanisms of interfering with mammalian hemostasis, presumably for the purpose of facilitating bloodfeeding. Adult **Ancylostoma** caninum worm extracts contain an activity that **inhibits platelet** aggregation and adhesion by blocking the function of two cell surface **integrin** receptors, Glycoprotein IIb/IIIa and **GPIa**/IIa. Using rpHPLC, the **hookworm platelet inhibitor** activities have been purified from protein extracts of

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A. caninum. Because the two **inhibitory** activities co-purified through multiple chromatographic steps, have similar molecular masses and share identical N-terminal as well as internal amino acid sequence **homology**, it is likely that they represent a single gene product. A cDNA corresponding to the purified **hookworm platelet inhibitor** (HPI) protein has been cloned from adult **A. caninum** RNA, and the translated amino acid sequence shows significant **homology** to Neutrophil **Inhibitory** Factor and **Ancylostoma** Secreted Proteins, suggesting that these related **hookworm** proteins represent a novel class of **integrin** receptor antagonists. Polyclonal antibodies raised against the **recombinant** HPI protein recognize corresponding native proteins in **A. caninum** extracts and excretory/secretory products, and immunohistochemistry data have identified the cephalic glands as the major source of the **inhibitor** within the adult **hookworm**. These data suggest that HPI is secreted by the adult stage of the parasite at the site of intestinal attachment. As such, it may represent a viable target for a **vaccine**-based strategy aimed at interfering with **hookworm** -induced gastrointestinal hemorrhage and iron deficiency anemia.

L25 ANSWER 3 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:615867 HCAPLUS
DOCUMENT NUMBER: 137:165271
TITLE: **Integrin**-binding fusion proteins of dendroaspin and anticoagulant proteins and their use in the treatment of clotting disorders
INVENTOR(S): Lu, Xinjie; Kakkar, Vijay Vir
PATENT ASSIGNEE(S): Trigen Limited, UK
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002063017	A2	20020815	WO 2002-GB500	20020205

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-267234P P 20010205
OTHER SOURCE(S): MARPAT 137:165271
AB Fusion proteins of an **integrin**-binding protein, esp. dendroaspin and a second protein are described for use in the targeted therapeutic delivery of proteins to blood vessels. The second moiety of the fusion protein is most often an anticoagulant protein for use in the treatment of clotting disorders. Chimeric genes encoding a fusion proteins of dendroaspin and the proteinase **inhibitor** NAP5 of **Ancylostoma** caninum was constructed and expressed in Escherichia coli. The proteins **inhibited ADP**-induced

Search completed by David Schreiber 308-4292

platelet aggregation at concns. of 260-500 nm, compared to 76-277 nM for dendroaspin and other snake venom anticoagulants. They also **inhibited** collagen-induced **platelet** aggregation. Dendroaspin did not **inhibit** factor Xa, but the fusion proteins **inhibited** it at 1.1-140.9 nM.

L25 ANSWER 4 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2002279705 MEDLINE
DOCUMENT NUMBER: 22013960 PubMed ID: 11880366
TITLE: Delineation of the key amino acids involved in neutrophil **inhibitory** factor binding to the I-domain supports a mosaic model for the capacity of **integrin** alphaMbeta 2 to recognize multiple ligands.
AUTHOR: Ustinov Valentin A; Plow Edward F
CORPORATE SOURCE: Joseph J. Jacobs Center for Thrombosis and Vascular Biology, and Department of Molecular Cardiology/NB50, The Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.
CONTRACT NUMBER: HL 66197 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 May 24) 277 (21) 18769-76.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020522
Last Updated on STN: 20030105
Entered Medline: 20020624

AB To gain insight into the mechanism by which the alpha(M)I-domain of **integrin** alpha(M)beta(2) interacts with multiple and unrelated ligands, the identity of the neutrophil **inhibitory** factor (NIF) recognition site was sought. A systematic strategy in which individual amino acid residues within three previously implicated segments were changed to those in the alpha(L)I-domain, which is structurally very similar but does not bind NIF, was implemented. The capacity of the resulting **mutants**, expressed as glutathione S-transferase fusion proteins, to recognize NIF was assessed. These analyses ultimately identified Asp(149), Arg(151), Gly(207), Tyr(252), and Glu(258) as critical for NIF binding. Cation binding, a function of the metal ion-dependent adhesion site (MIDAS) motif, was assessed by terbium luminescence to evaluate conformational perturbations induced by the mutations. All five **mutants** bound terbium with unaltered affinities. When the five residues were inserted into the alpha(L)I-domain, the chimera bound NIF with high affinity. Another ligand of alpha(M)beta(2), C3bi, which is known to use the same segments of the alpha(M)I-domain in engaging the receptor, failed to bind to the chimeric alpha(L)I-domain. Thus, the alpha(M)I-domain appears to present a mosaic of exposed amino acids within surface loops on its MIDAS face, and different ligands interact with different residues to attain high affinity binding.

L25 ANSWER 5 OF 67 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002127556 MEDLINE
DOCUMENT NUMBER: 21839046 PubMed ID: 11741914
TITLE: Molecular characterization of Ancylostoma **inhibitors** of coagulation factor Xa. **Hookworm** anticoagulant activity in vitro predicts parasite bloodfeeding in vivo.

Search completed by David Schreiber 308-4292

AUTHOR: **Harrison Lisa M**; Nerlinger Andrew; Bungiro Richard D; Cordova Jose Luis; Kuzmic Petr; Cappello Michael
CORPORATE SOURCE: Yale Child Health Research Center, Division of Infectious Diseases, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut 06520-8081, USA.
CONTRACT NUMBER: AI01299 (NIAID)
AI07404 (NIAID)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Feb 22) 277 (8) 6223-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF399710
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020227
Last Updated on STN: 20030105
Entered Medline: 20020424

AB Bloodfeeding hookworms, which currently infect over a billion people in the developing world, are a leading cause of gastrointestinal hemorrhage and iron deficiency anemia. The major anticoagulant **inhibitor** of coagulation factor Xa has been identified from the **hookworm** parasite Ancylostoma ceylanicum using reverse transcription PCR and 3'-rapid amplification of cDNA ends. This is the first anticoagulant cloned from a **hookworm** species for which humans are recognized permissive hosts. Despite approximately 50% amino acid similarity, A. ceylanicum anticoagulant peptide 1 (AceAP1) is both immunologically and mechanistically distinct from AcAP5, its **homologue** isolated from the dog **hookworm** Ancylostoma caninum. Studies using plasma clotting times and single stage chromogenic assays of factor Xa activity have demonstrated that the **recombinant** AceAP1 protein is substantially less potent than AcAP5 and that soluble whole worm protein extracts of adult A. ceylanicum possess less anticoagulant activity than extracts of A. caninum. These values correlate with previously reported differences in bloodfeeding capabilities between these two species of **hookworm**, suggesting that factor Xa **inhibitory** activity is predictive of **hookworm** bloodfeeding capabilities in vivo. These fundamental differences in the mechanism of action and immunoreactivity of the major anticoagulant virulence factors from related Ancylostoma **hookworm** species may have significant implications for human **vaccine** development.

L25 ANSWER 6 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2002:450261 SCISEARCH
THE GENUINE ARTICLE: 553NJ
TITLE: The parasitic hematophagous worm Haemonchus contortus **inhibits** human **platelet** aggregation and adhesion: Partial purification of a **platelet inhibitor**
AUTHOR: Crab A; Noppe W; Pelicaen C; Van Hoorelbeke K; Deckmyn H (Reprint)
CORPORATE SOURCE: Katholieke Univ Leuven, IRC, Lab Thrombosis Res, Campus Kortrijk, E Sabbelaan 53, B-8500 Kortrijk, Belgium (Reprint); Katholieke Univ Leuven, IRC, Lab Thrombosis Res, B-8500 Kortrijk, Belgium
COUNTRY OF AUTHOR: Belgium
SOURCE: THROMBOSIS AND HAEMOSTASIS, (MAY 2002) Vol. 87, No. 5, pp. 899-904.

Publisher: SCHATTAUER GMBH-VERLAG MEDIZIN NATURWISSENSCHAFTEN, HOLDERLINSTRASSE 3, D-70174 STUTTGART, GERMANY.
ISSN: 0340-6245.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Blood sucking parasites elaborate mechanisms to counteract the hemostatic system of their victim. Haemonchus contortus worms use several mechanisms directed against the normal **platelet** hemostatic function. **Platelet** adhesion onto collagen and fibrinogen, and the ristocetin-mediated interaction of von Willebrand Factor with glycoprotein (GP) Ib were **inhibited** by the protein extract of adult worms. Also **platelet** aggregation induced by collagen, **thrombin**, **ADP**, ristocetin or A23187 was **inhibited**. Although we obtained evidence for interference with fibrinogen binding to **GPIIb**/IIIa, the strongest **inhibition** was seen when the agonists collagen or **thrombin** were used, A small multi-subunit **inhibitor** of collagen-induced **platelet** aggregation was partially purified using anion exchange chromatography, gelfiltration and RP-HPLC. The **inhibitor** has a pI between 4 and 6.5, elutes with a molecular weight of 23,800 Da after gelfiltration, and is pail of the elaborate broad-spectrum antiplatelet activity that results in the potent synergistic anti-hemostatic cocktail produced by H. contortus.

L25 ANSWER 7 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2002146028 MEDLINE
DOCUMENT NUMBER: 21868257 PubMed ID: 11880306
TITLE: Time-dependent reversal of sepsis-induced PMN uptake and lung vascular injury by expression of CD18 antagonist.
AUTHOR: Xu Ning; Gao Xiao-Pei; Minshall Richard D; Rahman Arshad; Malik Asrar B
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, The University of Illinois, 835 S Wolcott Avenue, Chicago, IL 60612, USA.
CONTRACT NUMBER: HL-45638 (NHLBI)
HL-46350 (NHLBI)
HL-64573 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. LUNG CELLULAR AND MOLECULAR PHYSIOLOGY, (2002 Apr) 282 (4) L796-802.
Journal code: 100901229. ISSN: 1040-0605.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020307
Last Updated on STN: 20020412
Entered Medline: 20020411

AB We determined the time-dependent effects of conditional expression of neutrophil **inhibitory** factor (NIF), a specific 41-kDa CD18 **integrin** antagonist, on the time course of NIF expression and lung PMN (polymorphonuclear leukocyte) infiltration and vascular injury in a model of Escherichia coli-induced sepsis in mice. Studies were made in mice transduced with the E-selectin (ES) promoter-NIF construct (using liposomes) in which the NIF cDNA was driven by the inflammation- and endothelial cell-specific ES promoter. We observed time-dependent

expression of NIF in pulmonary vascular endothelium that paralleled the ES expression. Expression of both was evident at 1 h after E. coli challenge, peaked at 3-6 h, and returned to basal level within 48 h. We observed that increases in PMN uptake and transalveolar PMN migration induced by E. coli challenge were reversed in a time-dependent manner following NIF expression in mice. NIF expression also prevented the progression of lung vascular injury and edema formation following E. coli challenge. Thus the conditional expression of NIF using the ES promoter can reverse, in a time-dependent manner, lung PMN infiltration and vascular injury induced by gram-negative sepsis. The results support the model that initial engagement of CD18 **integrins** enables the further recruitment of additional PMN into lung tissues such that PMN continue to sequester and migrate after E. coli challenge.

L25 ANSWER 8 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2002:96309 SCISEARCH
THE GENUINE ARTICLE: 514UW
TITLE: Ancylostoma ceylanicum excretory/secretory protein 1: purification and molecular cloning of a major secretory protein from adult hookworms
AUTHOR: Bungiro R D (Reprint); **Harrison L M**; Cappello M
CORPORATE SOURCE: Yale Univ, Sch Med, Dept Pediat, Div Infect Dis, 464 Congress Ave, New Haven, CT 06520 USA (Reprint); Yale Univ, Sch Med, Dept Pediat, Div Infect Dis, New Haven, CT 06520 USA; Yale Univ, Sch Med, Dept Epidemiol & Publ Hlth, Div Infect Dis, New Haven, CT 06520 USA
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR AND BIOCHEMICAL PARASITOLOGY, (JAN 2002) Vol. 119, No. 1, pp. 147-151.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0166-6851.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 23

L25 ANSWER 9 OF 67 AGRICOLA Compiled and distributed by the National Agricultural Library of the Department of Agriculture of the United States of America. It contains copyrighted materials. All rights reserved. (2003) on STN
ACCESSION NUMBER: 2002:22419 AGRICOLA
DOCUMENT NUMBER: IND23260394
TITLE: Natural history of primary canine **hookworm** infections after three different oral doses of third-stage infective larvae of **Ancylostoma** caninum.
AUTHOR(S): Hotez, P.J.; Bin, Z.; Bethony, J.; Jin, Q.; Hawdon, J.M.; Young, H.A.; Simmens, S.; Hitzelberg, R.; Zook, B.C.
AVAILABILITY: DNAL (QL392.J68)
SOURCE: Journal of the Helminthological Society of Washington, Jan 2002. Vol. 69, No. 1. p. 72-80
Publisher: Lawrence, Kan. : The Society, c1990-
CODEN: JHSWE4; ISSN: 1049-233X
NOTE: Includes references
PUB. COUNTRY: Kansas; United States
DOCUMENT TYPE: Article
FILE SEGMENT: U.S. Imprints not USDA, Experiment or Extension
LANGUAGE: English

Search completed by David Schreiber 308-4292

L25 ANSWER 10 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:101291 HCAPLUS
DOCUMENT NUMBER: 134:161880
TITLE: cDNAs encoding the Flt-3 receptor ligand and there use as adjuvants in vector **vaccines**
INVENTOR(S): Hermanson, Gary George
PATENT ASSIGNEE(S): Vical Inc., USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001009303	A2	20010208	WO 2000-US20679	20000731
WO 2001009303	A3	20010816		

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-146170P P 19990730
AB A method of increasing the strength of the immune response of vector **vaccines** using an expression vector for the Flt3 ligand is described. The **vaccines** are made of independent non-integrating expression vectors: one encodes the antigen or a cytokine and the other encodes the Flt3 ligand. The present invention also provides a method broadly directed to improving immune response of a vertebrate in need of immunotherapy by administering in vivo, into a tissue of a vertebrate, a Flt-3 ligand-encoding polynucleotide and one or more antigen- or cytokine-encoding polynucleotides. The polynucleotides are incorporated into the cells of the vertebrate in vivo, and a prophylactically or therapeutically effective amt. of a Flt-3 ligand and one or more antigens is produced in vivo.

L25 ANSWER 11 OF 67 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001366135 MEDLINE
DOCUMENT NUMBER: 21320020 PubMed ID: 11426727
TITLE: Identification of a collagen-binding protein from **Necator** americanus by using a cDNA-expression phage display library.
AUTHOR: Viaene A; Crab A; Meiring M; Pritchard D; Deckmyn H
CORPORATE SOURCE: Laboratory for Thrombosis Research, IRC, KU Leuven Campus Kortrijk, Belgium.
SOURCE: JOURNAL OF PARASITOLOGY, (2001 Jun) 87 (3) 619-25.
Journal code: 7803124. ISSN: 0022-3395.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705
AB A phage display library was made starting from a cDNA library from the hematophagous human parasite **Necator** americanus. The cDNA library was transferred by polymerase chain reaction (PCR) cloning into phage display vectors (phagemids), using specially designed primers such

that proteins would be expressed as fusions with the C-terminal part of the phage coat protein pVI. The vectors used are multicloning site **variants** of the original pDONG vectors described by Jespers et al. (1995). Electroporation of the ligation mixtures into electrocompetent Escherichia coli TGI cells yielded 3 x 10(8) pG6A, 1.9 x 10(8) pG6B, and 1 x 10(8) pG6C transfectants for **N. americanus**. The final libraries consisted of a mix of equal numbers of insert-containing phages from the A, B, and C libraries. Selection of phages for binding to human collagen was performed. Four rounds of panning on human collagens I and III resulted in a significant enrichment of collagen-binding phages from the **N. americanus** libraries. PCR analysis revealed various insert lengths; however, sequence determination indicated that all phages contained the same protein, albeit with different poly-A tail lengths. The encoded protein itself is a 135-amino acid protein (15 kDa), with no apparent **homology** to any other known protein. Next the protein was recloned into E. coli using the pET-15b-vector. Upon isopropyl-1-thio-beta-D-galactopyranoside induction, the **recombinant** protein, rNecH1, could be recovered by urea treatment from inclusion bodies. The rNecH1 protein binds to different collagens: human I > rat I > human III = calf skin I in a specific, dose-dependent, and saturable manner.

L25 ANSWER 12 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:427144 HCAPLUS
DOCUMENT NUMBER: 136:100809
TITLE: **Vaccination** with neutrophil **inhibitory** factor reduces the fecundity of the **hookworm Ancylostoma** ceylanicum
AUTHOR(S): Ali, F.; Brown, A.; Stanssens, P.; Timothy, L. M.; Seule, M. R.; Pritchard, D. I.
CORPORATE SOURCE: The Boots Science Institute, University of Nottingham, Nottingham, NG7 2RD, UK
SOURCE: Parasite Immunology (2001), 23(5), 237-249
CODEN: PAIMD8; ISSN: 0141-9838
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Neutrophil **inhibitory** factor (NIF), a protein isolated from hookworms of the genus **Ancylostoma**, **inhibits** CD11b/18-dependent leukocyte function, binding to the I domain of CD11b. Historically, NIF was serendipitously isolated from whole worm exts. during a search for novel antihaemostatic agents, and little is known of its source or biol. significance to the parasite. NIF has also been identified as a possible **hookworm vaccine** candidate. **Ancylostoma** ceylanicum **recombinant** NIF, expressed in its active form in Pichia pastoris, was purified and its functional activity confirmed using neutrophil adhesion assays and confirmatory immunoassay. **Recombinant** NIF was subsequently used in **vaccination** trials in the **A. ceylanicum**-hamster model system for human **hookworm** infection. **Vaccinated** and challenged animals were not protected in terms of worm burden or haematocrit values, despite the presence of high levels of specific antibody against NIF. However, adult worms resident in **vaccinated** animals showed a significant redn. in fecundity (85.8% by day 21 postinfection), indicating a degree of protection against subsequent transmission by **vaccination**. These data indicate that targeted **vaccination** with **recombinant** subunit material, derived from a known and effective immune suppressant secreted by the parasite, may offer partial protection against the transmission of **hookworm**

Search completed by David Schreiber 308-4292

[redacted]

infection. Furthermore, the authors can also report that a biol. activity characteristic of NIF is detectable in the secretions of **A. ceylanicum** using two complementary bioassays. Complete neutralization of this secreted activity by **vaccination** in combination with other **vaccine** candidates may result in improved protection against **A. ceylanicum** infection.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 13 OF 67 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2001220193 MEDLINE
DOCUMENT NUMBER: 21137484 PubMed ID: 11240905
TITLE: A calreticulin-like molecule from the human **hookworm Necator** americanus interacts with C1q and the cytoplasmic signalling domains of some **integrins**.
AUTHOR: Kasper G; Brown A; Eberl M; Vallar L; Kieffer N; Berry C; Girdwood K; Eggleton P; Quinnell R; Pritchard D I
CORPORATE SOURCE: The Boots Institute, School of Pharmaceutical Sciences, University of Nottingham, UK.
SOURCE: PARASITE IMMUNOLOGY, (2001 Mar) 23 (3) 141-52. Journal code: 7910948. ISSN: 0141-9838.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010524

AB Calreticulin was recently identified as a **hookworm** (**Necator** americanus) allergen, implying secretion, and contact with cells of the immune system, or significant worm attrition in the tissues of the host. As human calreticulin has been shown to bind to and neutralize the haemolytic activity of the complement component C1q, and to be putatively involved in **integrin**-mediated intracellular signalling events in **platelets**, it was of interest to determine whether a calreticulin from a successful nematode parasite of humans, with known immune modulatory and antihaemostatic properties, exhibited a capacity to interfere with complement activation and to interact with **integrin** domains associated with cell signalling in **platelets** and other leucocytes. We can now report that **recombinant** calreticulin failed to demonstrate significant calcium binding capacity, which is a hallmark of calreticulins in general and may indicate inappropriate folding following expression in a prokaryote. Nevertheless, **recombinant** calreticulin retained sufficient molecular architecture to bind to, and **inhibit** the haemolytic capacity of, human C1q. Furthermore, **recombinant** calreticulin reacted in surface plasmon resonance analysis (SPR) with peptides corresponding to cytoplasmic signalling domains of the **integrins** alphaIIb and alpha5, in a calcium independent manner. SPR was also used to ratify the specificity of a polyclonal antibody to **hookworm** calreticulin, which was then used to assess the stage specificity of expression of the native molecule (in comparison with reverse transcriptase-polymerase chain reaction), to indicate its apparent secretion, and to purify native calreticulin from worm extracts by affinity chromatography. This development will allow the functional tests described above to be repeated for native calreticulin, to ascertain its role in the host-parasite relationship.

Search completed by David Schreiber 308-4292

[redacted]

L25 ANSWER 14 OF 67 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001297927 MEDLINE
DOCUMENT NUMBER: 21273147 PubMed ID: 11377744
TITLE: Ancylostoma caninum anticoagulant peptide-5: immunolocalization and in vitro neutralization of a major **hookworm** anti-thrombotic.
AUTHOR: **Harrison L M**; Cordova J L; Cappello M
CORPORATE SOURCE: Infectious Diseases Section, Departments of Pediatrics and Epidemiology and Public Health, Child Health Research Center, Yale University School of Medicine, 06520-8081, New Haven, CT, USA.
CONTRACT NUMBER: AI01299 (NIAID)
SOURCE: MOLECULAR AND BIOCHEMICAL PARASITOLOGY, (2001 Jun) 115 (1) 101-7.
Journal code: 8006324. ISSN: 0166-6851.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011022
Last Updated on STN: 20011022
Entered Medline: 20011018

AB **Hookworm** infection is a major cause of gastrointestinal blood loss and iron deficiency anemia in the developing world. Recently two major anticoagulant serine protease **inhibitors** have been identified and cloned from adult Ancylostoma caninum hookworms. One of these, A. caninum anticoagulant peptide 5 (AcAP5), is a potent and specific **inhibitor** of human coagulation factor Xa. A polyclonal IgG has been purified from rabbits **immunized** with **recombinant** AcAP5 using affinity chromatography. Using immunohistochemistry, the polyclonal alpha-rAcAP5 IgG localized to the cephalic or amphidial glands, confirming previous biochemical studies that had identified this secretory gland as the primary source of anticoagulant activity in the adult worm. This polyclonal IgG also neutralized the **inhibitory** activity of **recombinant** and native AcAP using a single stage chromogenic assay of coagulation factor Xa activity. In addition, the polyclonal IgG also neutralized the anticoagulant activity of native and **recombinant** AcAP5 as measured by the activated partial thromboplastin time clotting assay. Importantly, this neutralizing activity is species specific, as the polyclonal IgG failed to neutralize the anticoagulant activity of A. ceylanicum. Taken together, these data suggest that the **hookworm** anticoagulant AcAP5 represents a viable target for future **immunization** strategies aimed at **inhibiting** the ability of the adult **hookworm** to feed on blood in vivo.

L25 ANSWER 15 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2001212564 MEDLINE
DOCUMENT NUMBER: 21084202 PubMed ID: 11215490
TITLE: A case of **hookworm** infestation with dissociation values between FDP-E and FDP-D dimer.
AUTHOR: Nakagoshi R; Oguchi H; Ishii E; Ishikawa S; Higuchi Y; Muramatsu K; Okumura N; Ogiso Y
CORPORATE SOURCE: Division of Clinical Pathology, Nagano Children's Hospital, Minami-azumi-gun, Nagano-pref. 399-8288.
SOURCE: RINSHO BYORI. JAPANESE JOURNAL OF CLINICAL PATHOLOGY, (2001 Jan) 49 (1) 82-6.

Search completed by David Schreiber 308-4292

[redacted]

Journal code: 2984781R. ISSN: 0047-1860.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB We previously reported a five-year-old girl showing bleeding tendency and transient morphological and functional **platelet** abnormalities probably due to a **hookworm, Necator** Americanus, infestation. In this report, we describe the rarely accelerated fibrinogenolysis and/or fibrinolysis in this patient whose value of fibrinogen and/or fibrin degradation products(FDP) determined with an FDP-E assay was much higher than that determined with a D-dimer assay. Namely, on day-1 and day-13 of hospitalization, her D-dimer values were only 10 to 20% of the prospected values from FDP-E values. We speculated this phenomenon was induced by circulating protease(-like) agent(s) produced by **hookworm**, because the only slightly participation of plasmin and/or granulocyte elastase was evaluated by the determination of enzyme-**inhibitor** complexes. And the other possibility of fibrinogen degradation by blast- or tumor-associated protease was excluded by the clinical manifestations and primary disorders. In conclusion, we report a very rare case with the accelerated fibrinogenolysis and/or fibrinolysis in a patient with the **hookworm** infestation. We are interested in the mechanism that manifested the patient's bleeding tendency accompanied with morphological and functional **platelet** abnormalities.

L25 ANSWER 16 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:250831 HCAPLUS
DOCUMENT NUMBER: 135:17898
TITLE: Acquired **platelet** dysfunction with eosinophilia in children in the south of Thailand
AUTHOR(S): Laosombat, Vichai; Wongchanchailert, Malai; Sattayasevana, Benjamas; Kietthubthew, Suparp; Wiriyasateinkul, Aranya
CORPORATE SOURCE: Division of Pediatric Hematology and Oncology, Faculty of Medicine, Prince of Songkla University, Songkla, 90110, Thailand
SOURCE: Platelets (2001), 12(1), 5-14
CODEN: PLTEEF; ISSN: 0953-7104
PUBLISHER: Carfax Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB One hundred and sixty-eight children aged 13 mo to 12.6 yr with acquired **platelet** dysfunction with eosinophilia (APDE) were studied. The male to female ratio was 1.15:1. All of the children were in good health and no history of any drug ingestion was detected. All of the children had widespread spontaneous bruising on the extremities, body and face off and on. Severe bleeding symptoms were detected in 8% of these patients. The no. of **platelets** in these children was within the normal range but the **platelet** morphol. was abnormal in all of them. Eosinophilia was detected in 86% of these children. Prolonged bleeding time was detected in 53% of these patients. Abnormal **platelet** adhesiveness was found in 33% of cases. Abnormal **platelet** aggregation induced by collagen was the most sensitive test in these patients. Abnormal **ADP** release from the **platelets** was

detected in these patients by the absence of a second wave of aggregation during stimulation of PRP by **ADP** or **epinephrine**. Abnormal or no ATP secretion from the **platelets** during stimulation by **ADP**, **epinephrine** or collagen was detected in these patients. Ristocetin-induced **platelet** aggregation was normal in these children. Decreased or absence of **platelet** dense granules by TEM study was detected in some patients. These changes in **platelet** functions and morphol. may be due to acquired storage pool deficiency of the **platelet**. Parasitic infection was detected in 56% of these children. About 83% of these children with APDE had serum total IgE higher than 100 IU/mL. There was no correlation between the no. of eosinophils and serum total IgE and the severity of bleeding symptoms. The majority of children with APDE did not receive any treatment except those who had severe bleeding symptoms which required **platelet** conc. to stop bleeding. In more than 90% of the patients, the bruising or ecchymosis disappeared within 6 mo and the abnormal **platelet** functions returned to normal within 4 mo. Recurrence of these bleeding syndromes was detected in 7% of the children.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 17 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:707193 HCAPLUS
DOCUMENT NUMBER: 133:286422
TITLE: **Hookworm platelet** aggregation **inhibitor**
INVENTOR(S): Cappello, Michael; **Chadderdon, Robert C.**; **Del Valle, Antonio**; **Harrison, Lisa M.**
PATENT ASSIGNEE(S): Yale University, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000058341	A1	20001005	WO 2000-US8519	20000330
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1165598	A1	20020102	EP 2000-918509	20000330
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539817	T2	20021126	JP 2000-608041	20000330

PRIORITY APPLN. INFO.: US 1999-127239P P 19990331
WO 2000-US8519 W 20000330

AB An **inhibitor** of **platelet** aggregation and adhesion is purified and characterized from sol. protein exts. of adult **Ancylostoma** caninum hookworms and then cloned and sequenced. The **inhibitor** blocks **platelet** aggregation in response to a

[redacted]

variety of agonists, interfering with the binding of at least one cell surface **integrin** with its resp. ligand. Embodiments include **inhibition** of the binding of fibrinogen to cell surface **integrin GPIIb**/IIIa (.alpha.IIb.beta.3) and **inhibition** of the binding of collagen to cell surface **integrin GPIa**/IIa (.alpha.2.beta.1). Medical and veterinary pharmaceutical and immunol. compns. contg. the **platelet inhibitor**, and methods of using it, are described.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 18 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:531682 HCAPLUS
DOCUMENT NUMBER: 133:131741
TITLE: Serine proteinase **inhibitors** and anticoagulant proteins from Ancyclostoma caninum
INVENTOR(S): Vlasuk, George Phillip; Stanssens, Patrick Eric Hugo; Messens, Joris Hilda Lieven; Lauwereys, Marc Josef; Laroche, Yves Rene; Jespers, Laurent Stephane; Gansemans, Yannick Georges Jozef; Moyle, Matthew; Bergum, Peter W.
PATENT ASSIGNEE(S): Corvas International, Inc., USA
SOURCE: U.S., 199 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6096877	A	20000801	US 1999-249461	19990212

PRIORITY APPLN. INFO.: US 1999-249461 19990212
OTHER SOURCE(S): MARPAT 133:131741
AB Proteins which have activity as anticoagulants or serine protease **inhibitors** and have at least one NAP (nematode anticoagulant protein) domain and are described. Certain of these proteins have factor Xa **inhibitory** activity and others have activity as **inhibitors** of factor VIIa/TF. These proteins can be isolated from natural sources such as the nematode Ancyclostoma caninum, chem. synthesized or made by expression of the cloned gene. Purifn. of two such proteins from **A. caninum**, cloning and expression of cDNAs encoding them, and use of the cDNAs to clone corresponding cDNAs from **Necator** americanus are described. The proteins had a Ki for factor Xa amidolytic activity of 43.+-.5 or 996.+-.65 pM and for prothrombin of 144.+-.15 and 207.+-.40 pM resp. The proteins were also effective in preventing thrombotic occlusion in vivo in the rat model of FeCl3-induced **platelet**-dependent arterial thrombosis.
REFERENCE COUNT: 138 THERE ARE 138 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 19 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:492067 HCAPLUS
DOCUMENT NUMBER: 133:116714
TITLE: Serine proteinase **inhibitors** and anticoagulant proteins from Ancyclostoma caninum
INVENTOR(S): Vlasuk, George Phillip; Stanssens, Patrick Eric Hugo; Messens, Joris Hilda Lieven; Lauwereys, Marc Josef;

Laroche, Yves Rene; Jespers, Laurent Stephane; Gansemans, Yannick Georges Jozef; Moyle, Matthew; Bergum, Peter W.
PATENT ASSIGNEE(S): Corvas International, Inc., USA
SOURCE: U.S., 201 pp., Cont.-in-part of U.S. 5,872,098. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6090916	A	20000718	US 1997-809455	19970417
US 5945275	A	19990831	US 1994-326110	19941018
US 5863894	A	19990126	US 1995-465380	19950605
US 5866542	A	19990202	US 1995-486397	19950605
US 5866543	A	19990202	US 1995-486399	19950605
US 5872098	A	19990216	US 1995-461965	19950605
WO 9612021	A2	19960425	WO 1995-US13231	19951017
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MW, MX, NO, NZ, PL, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6534629	B1	20030318	US 1999-249473	19990212
US 2003113890	A1	20030619	US 2000-498272	20000204

PRIORITY APPLN. INFO.:
US 1994-326110 A2 19941018
US 1995-461965 A2 19950605
US 1995-465380 A2 19950605
US 1995-486397 A2 19950605
US 1995-486399 A2 19950605
WO 1995-US13231 W 19951017
US 1997-809455 A1 19970417

OTHER SOURCE(S): MARPAT 133:116714

AB Proteins which have activity as anticoagulants or serine protease **inhibitors** and have at least one NAP (nematode anticoagulant protein) domain and are described. Certain of these proteins have factor Xa **inhibitory** activity and others have activity as **inhibitors** of factor VIIa/TF. These proteins can be isolated from natural sources such as the nematode Ancylostoma caninum, chem. synthesized or made by expression of the cloned gene. Purifn. of two such proteins from **A. caninum**, cloning and expression of cDNAs encoding them, and use of the cDNAs to clone corresponding cDNAs from **Necator** americanus are described. The proteins had a Ki for factor Xa amidolytic activity of 43.+-.5 or 996.+-.65 pM and for prothrombin of 144.+-.15 and 207.+-.40 pM resp. The proteins were also effective in preventing thrombotic occlusion in vivo in the rat model of FeCl3-induced **platelet**-dependent arterial thrombosis.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 20 OF 67 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001021344 MEDLINE
DOCUMENT NUMBER: 20449012 PubMed ID: 10893410
TITLE: A broad spectrum Kunitz type serine protease **inhibitor** secreted by the **hookworm** Ancylostoma ceylanicum.

Search completed by David Schreiber 308-4292

[redacted]

Kam 09/937,555

AUTHOR: Milstone A M; **Harrison L M**; Bungiro R D; Kuzmic P; Cappello M
CORPORATE SOURCE: Infectious Diseases Section, Yale Child Health Research Center, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut 06520-8081, USA.
CONTRACT NUMBER: K11 AI01299 (NIAID)
P30 HD2775 (NICHD)
T32 AI07404 (NIAID)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Sep 22) 275 (38) 29391-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF172651
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001103

AB Although blood-feeding hookworms infect over a billion people worldwide, little is known about the molecular mechanisms through which these parasitic nematodes cause gastrointestinal hemorrhage and iron deficiency anemia. A cDNA corresponding to a secreted Kunitz type serine protease **inhibitor** has been cloned from adult Ancylostoma ceylanicum **hookworm** RNA. The translated sequence of the A. ceylanicum Kunitz type **inhibitor** 1 (AceKI-1) cDNA predicts a 16-amino acid secretory signal sequence, followed by a 68-amino acid mature protein with a molecular mass of 7889 daltons. **Recombinant** protein (rAceKI-1) was purified from induced lysates of Escherichia coli transformed with the rAceKI-1/pET 28a plasmid, and in vitro studies demonstrate that rAceKI-1 is a tight binding **inhibitor** of the serine proteases chymotrypsin, pancreatic elastase, neutrophil elastase, and trypsin. AceKI-1 **inhibitory** activity is present in soluble protein extracts and excretory/secretory products of adult hookworms but not the infective third stage larvae. The native AceKI-1 **inhibitor** has been purified to homogeneity from soluble extracts of adult A. ceylanicum using size exclusion and reverse-phase high pressure liquid chromatography. As a potent **inhibitor** of mammalian intestinal proteases, AceKI-1 may play a role in parasite survival and the pathogenesis of **hookworm** anemia.

L25 ANSWER 21 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2000:904193 SCISEARCH
THE GENUINE ARTICLE: 376PZ
TITLE: Eotaxin is specifically cleaved by **hookworm** metalloproteases preventing its action in vitro and in vivo
AUTHOR: Culley F J (Reprint); Brown A; Conroy D M; Sabroe I; Pritchard D I; Williams T J
CORPORATE SOURCE: IMPERIAL COLL SCH MED, DIV BIOMED SCI, LEUKOCYTE BIOL SECT, SIR ALEXANDER FLEMING BLDG, S KENSINGTON, LONDON SW7 2AZ, ENGLAND (Reprint); UNIV NOTTINGHAM, INST PHARMACEUT SCI, NOTTINGHAM NG7 2RD, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: JOURNAL OF IMMUNOLOGY, (1 DEC 2000) Vol. 165, No. 11, pp. 6447-6453.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.

Search completed by David Schreiber 308-4292

[redacted]

ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 49

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Eotaxin is a potent eosinophil chemoattractant that acts selectively through CCR3, which is expressed on eosinophils, basophils, mast cells, and Th2-type T cells, This arm of the immune system is believed to have evolved to control helminthic parasites. We hypothesized that helminths may employ mechanisms to **inhibit** eosinophil recruitment, to prolong worm survival in the host. We observed that the excretory/secretory products of the **hookworm Necator** americanus **inhibited** eosinophil recruitment in vivo in response to eotaxin, but not leukotriene B-4, a phenomenon that could be prevented by the addition of protease **inhibitors**. Using Western blotting, **N, americanus** supernatant was shown to cause rapid proteolysis of eotaxin, but not IL-8 or eotaxin-2, **N, americanus** homogenate was fractionated by gel filtration chromatography, and a FAGS-based bioassay measured the ability of each fraction to **inhibit** the activity of a variety of chemokines, This resulted in two peaks of eotaxin-degrading activity, corresponding to similar to 15 and 50 kDa molecular mass. This activity was specific for eotaxin, as responses to other agonists tested were unaffected. Proteolysis of eotaxin was prevented by EDTA and phenanthroline, indicating that metalloprotease activity was involved. Production of enzymes inactivating eotaxin may be a strategy employed by helminths to prevent recruitment and activation of eosinophils at the site of infection. As such this represents a novel mechanism of regulation of chemokine function in vivo. The existence of CCR3 ligands other than eotaxin (e.g., eotaxin-2) may reflect the evolution of host counter measures to parasite defense systems.

L25 ANSWER 22 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2000:419042 SCISEARCH
THE GENUINE ARTICLE: 298TM
TITLE: Cloning, expression and characterization of a novel protease **inhibitor** from bloodfeeding **hookworm**
AUTHOR: Milstone A M (Reprint); **Harrison L M**; Cappello M
CORPORATE SOURCE: YALE UNIV, SCH MED, DEPT PEDIAT, INFECT DIS SECT, NEW HAVEN, CT 06510; YALE UNIV, SCH MED, DEPT EPIDEMIOL & PUBL HLTH, INFECT DIS SECT, NEW HAVEN, CT 06510
COUNTRY OF AUTHOR: USA
SOURCE: PEDIATRIC RESEARCH, (APR 2000) Vol. 47, No. 4, Part 2, Supp. [S], pp. 1600-1600.
Publisher: INT PEDIATRIC RESEARCH FOUNDATION, INC, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0031-3998.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L25 ANSWER 23 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:322092 BIOSIS
DOCUMENT NUMBER: PREV200100322092
TITLE: Identification of amino acid residues within aMb2 required for recognition of a specific and high affinity ligand,

Search completed by David Schreiber 308-4292

NIF.
AUTHOR(S): Ustinov, Valentin A.; Plow, Edward F.
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 611a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Engagement of the alphaMbeta2 (CD11b/CD18, Mac-1) **integrin** on neutrophils supports their adhesion to vascular endothelial cells and their subsequent migration to the sites of inflammation. Such adhesion, as well as other functional responses, are blocked by a specific ligand for alphaMbeta2, neutrophils **inhibitory** factor (NIF), a **hookworm**-derived glycoprotein. This high affinity ligand binds directly to the alphaMI-domain (an inserted region of apprx 200 amino acid residues within the alphaM subunit). Three specific segments, Pro147-Arg152, Pro201-Lys217, and Asp248-Arg261 on the face of the alphaMI-domain containing the Metal Ion Dependent Adhesion Site (MIDAS) were implicated in NIF binding by a **homologous** scanning mutagenesis approach. To precisely define the molecular basis for binding of this model ligand to alphaMbeta2, the individual amino acid residues within these segments were changed to those in the alphaLI-domain, which is structurally very similar to the alphaMI-domain but does not bind NIF. First, sets of three amino acid residues within the segments were mutated to the corresponding alphaLI-domain residues, and the capacity of the resulting **mutants**, expressed as GST-fusion proteins in E. coli, to bind NIF was assessed. Of the 13 triple **mutants**, 5 lost their ability to bind NIF with high affinity. Second, in those triple **mutants** with reduced affinity for NIF, every individual amino acid residue was changed. The summary of these data identifies residues, D149, R151, G207, and E258 within alphaMI-domain as critical to NIF binding. The mutations at these positions reduced the affinities of the alphaMI-domain by 2-5.5-fold. The cation binding function of the MIDAS motif was assessed by terbium luminescence as a means to evaluate conformational perturbations induced by the mutations. All five **mutants** bound terbium with unaltered affinities. These data suggest that contact of five key residues, lying in close proximity to the cation binding site, are critical for high affinity binding of NIF. Taken together, distant contact points are needed to impart high affinity binding of ligands to alphaMbeta2.

L25 ANSWER 24 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2000:447177 SCISEARCH
THE GENUINE ARTICLE: 322PP
TITLE: Antithrombotic efficacy of single subcutaneous administration of a **recombinant** nematode anticoagulant peptide (rNAP5) in a canine model of coronary artery thrombolysis
AUTHOR: Rebello S S (Reprint); Blank H S; Lucchesi B R
CORPORATE SOURCE: AVENTIS PHARMA, CARDIOVASC BIOL, NW4, 500 ARCOLA RD, COLLEGEVILLE, PA 19426 (Reprint); UNIV MICHIGAN, SCH MED, DEPT PHARMACOL, ANN ARBOR, MI 48109
COUNTRY OF AUTHOR: USA
SOURCE: THROMBOSIS RESEARCH, (15 JUN 2000) Vol. 98, No. 6, pp. 531-540.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD,

Search completed by David Schreiber 308-4292

LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
ISSN: 0049-3848.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 23

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We examined the adjunctive benefit of **recombinant** nematode anticoagulant peptide (rNAP5), a factor Xa **inhibitor**, in a canine model of **recombinant** (rt)-PA-induced thrombolysis, In anesthetized dogs, a stable occlusive thrombus was formed by electrolytic injury of the vessel wall, after which the animals were administered rt-PA (1.44 mg/kg, i.v.) and rNAP5 (0.1 mg/kg, s.c,; n = 13), or rt-PA plus vehicle (1-2 ml, s.c,; n = 13), Hemodynamic and coagulation parameters were monitored for 360 minutes. Single subcutaneous administration of rNAP5 resulted in a prolonged and sustained increase in the activated partial thromboplastin time (>10-fold), whereas prothrombin time was unchanged. The template bleeding time was not altered significantly throughout the protocol (maximum 1.4-fold). The incidence of reperfusion was similar in the two groups with a trend toward faster reperfusion in the rNAP5 group (34+/-4 minutes) compared to the vehicle group (63+/-15 minutes; p = 0.07). After reperfusion, 80% of the vessels in the vehicle group reoccluded, whereas only 14% of vessels reoccluded in the rNAP5-treated group. Times to reocclusion were 65+/-21 minutes and 221 +/-28 minutes, respectively (p<0.05). Single subcutaneous administration of rNAP5 sustained the coronary artery blood flow after reperfusion, such that at the end of protocol the flow was 47% of the preocclusion value as compared to the vehicle group in which the flow was 11% (p<0.05). Cyclic flow reductions were most prominent during rt-PA-induced reperfusion and were similar in both groups. The results indicate that a single subcutaneous administration of rNAP5 provides a sustained antithrombotic effect in maintaining the coronary artery patency during rt-PA-induced thrombolysis, (C) 2000 Elsevier Science Ltd. All rights reserved.

L25 ANSWER 25 OF 67 MEDLINE on STN

ACCESSION NUMBER: 2000457356 MEDLINE
DOCUMENT NUMBER: 20438708 PubMed ID: 10980906
TITLE: Novel **inhibitors** of factor X for use in cardiovascular diseases.
AUTHOR: Spencer F A; Becker R C
CORPORATE SOURCE: Cardiovascular Thrombosis Research Center, UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655, USA.
SOURCE: CURRENT CARDIOLOGY REPORTS, (2000 Sep) 2 (5) 395-404. Ref: 56
Journal code: 100888969. ISSN: 1523-3782.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928

AB The complementary roles of **platelets** and **thrombin** in the pathophysiology of acute coronary syndromes suggests that for treatment to be effective, both mediators must be targeted. Although

[redacted]

great strides have been made in the development of antiplatelet therapies, attempts to **inhibit thrombin** have been less successful. Unfractionated heparin is limited by a number of pharmacologic shortcomings as well as an inability to meaningfully suppress **thrombin** generation. The low molecular weight heparins have yielded encouraging results in large-scale clinical trials, but it remains unclear whether their benefit stems from a superior pharmacologic profile to unfractionated heparin or is determined by an enhanced ability to suppress **thrombin** generation (by virtue of a direct anti-Xa effect). Regardless, investigators have become increasingly interested in factor Xa as a potential target for antithrombotic therapy. A number of naturally occurring Xa antagonists have been identified. Work with **recombinant** forms of these proteins confirms that factor Xa **inhibition** can suppress **thrombin** generation in a variety of animal thrombosis models. Accordingly, a number of synthetic direct and indirect Xa antagonists are under development for the prevention and treatment of thrombotic disorders. The following review summarizes the evolution of factor Xa antagonists.

L25 ANSWER 26 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:197695 BIOSIS
DOCUMENT NUMBER: PREV200000197695
TITLE: Cloning, expression and characterization of a novel protease **inhibitor** from bloodfeeding **hookworm**.
AUTHOR(S): Milstone, Aaron M. (1); **Harrison, Lisa M. (1)**; Cappello, Michael (1)
CORPORATE SOURCE: (1) Section of Infectious Diseases, Depts. of Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT USA
SOURCE: Pediatric Research, (April, 2000) Vol. 47, No. 4 Part 2, pp. 271A.
Meeting Info.: Joint Meeting of the Pediatric Academic Societies and the American Academy of Pediatrics. Boston, Massachusetts, USA May 12-16, 2000 American Academy of Pediatrics
. ISSN: 0031-3998.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 27 OF 67 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000419088 MEDLINE
DOCUMENT NUMBER: 20387074 PubMed ID: 10926878
TITLE: beta(2)-**Integrin** blockade driven by E-selectin promoter prevents neutrophil sequestration and lung injury in mice.
AUTHOR: Xu N; Rahman A; Minshall R D; Tiruppathi C; Malik A B
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, University of Illinois, Chicago, IL 60612-7343, USA.
CONTRACT NUMBER: HL27016 (NHLBI)
HL45638 (NHLBI)
HL60678 (NHLBI)
+
SOURCE: CIRCULATION RESEARCH, (2000 Aug 4) 87 (3) 254-60.
Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

Search completed by David Schreiber 308-4292

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000906

AB Interaction of CD11/CD18 beta(2) **integrins** on polymorphonuclear leukocytes (PMNs) with their counterreceptor, intercellular adhesion molecule-1, on the surface of vascular endothelial cells is a critical event mediating stable PMN adhesion and migration across the pulmonary vascular endothelial barrier. Neutrophil **inhibitory** factor (NIF), a 41-kDa glycoprotein isolated from the canine **hookworm** (**Ancylostoma** caninum), binds to the I domain of CD11a and CD11b and **inhibits** beta(2) **integrin**-dependent PMN adhesion. We describe a novel strategy using the endothelial cell-specific E-selectin promoter to induce NIF expression in an inflammation-specific manner in pulmonary vascular endothelial cells. A construct containing NIF cDNA driven by the inducible endothelial cell-specific E-selectin promoter (pESNIF) was transfected into human pulmonary artery endothelial cells (HPAECs). Lipopolysaccharide challenge (known to activate E-selectin) resulted in NIF mRNA and protein expression in transfected HPAECs. NIF expression induced by the E-selectin promoter prevented PMN adhesion to the activated HPAECs, whereas PMNs adhered avidly to activated HPAECs in the absence of NIF expression. To address the utility of this approach in conditionally preventing in vivo PMN sequestration, we injected mice intravenously with cationic liposomes containing the pESNIF construct. Analysis of lung tissue showed that intraperitoneal challenge of Escherichia coli resulted in NIF expression. Inflammation-specific NIF expression induced by the E-selectin promoter prevented lung PMN sequestration and vascular injury induced by E coli challenge. These studies suggest the feasibility of conditionally blocking beta(2) **integrin** function at sites where the endothelium is activated and thereby of locally preventing PMN activation and migration responses that lead to tissue inflammation.

L25 ANSWER 28 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:142254 BIOSIS
DOCUMENT NUMBER: PREV200200142254
TITLE: Cloning and expression of a **platelet** glycoprotein IIb/IIIa **inhibitor** from bloodfeeding hookworms.
AUTHOR(S): **Del Valle, A. (1); Harrison, L. M. (1)**; Cappello, M. (1)
CORPORATE SOURCE: (1) Yale University School of Medicine, New Haven, CT USA
SOURCE: Journal of Investigative Medicine, (March, 2000) Vol. 48, No. 2, pp. 219A. http://www.jinvmed.com/. print.
Meeting Info.: Eastern Society for Pediatric Research
ISSN: 1081-5589.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 29 OF 67 MEDLINE on STN
ACCESSION NUMBER: 2000397213 MEDLINE
DOCUMENT NUMBER: 20370158 PubMed ID: 10914492
TITLE: LFA-1 (CD11a/CD18) triggers hydrogen peroxide production by canine neutrophils.
AUTHOR: Lu H; Ballantyne C; Smith C W
CORPORATE SOURCE: Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas, USA.
CONTRACT NUMBER: AI19031 (NIAID)
ES06091 (NIEHS)

Search completed by David Schreiber 308-4292

HL42550 (NHLBI)
SOURCE: JOURNAL OF LEUKOCYTE BIOLOGY, (2000 Jul) 68 (1) 73-80.
Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000817

AB The respiratory burst of neutrophils stimulated by chemotactic factors is markedly augmented by Mac-1-dependent adhesion such as the interaction of Mac-1 (CD11b/CD18) with intercellular adhesion molecule-1 (ICAM-1; CD54) expressed on the surface of parenchymal cells (e.g., cardiac myocytes). In the current study, we evaluate the hypothesis that lymphocyte function-associated antigen-1 (LFA-1; CD11a/CD18) can also trigger the respiratory burst in neutrophils. To isolate LFA-1/ICAM-1 interactions from Mac-1/ ICAM-1 interactions, full-length chimeric ICAM-1 was developed and expressed in L cells with domains 1 and 2 from canine ICAM-1 and domains 3-5 from human ICAM-1 (C1,2;H3-5). We have shown that canine neutrophils do not bind to human ICAM-1. We demonstrated that chimeric ICAM-1 C1,2;H3-5 supported only LFA-1-dependent adhesion of canine neutrophils and that such adhesion triggered rapid onset of H2O2 production from canine neutrophils. The following seven experimental conditions distinguished LFA-1-dependent H2O2 production from Mac-1-dependent production: It did not require exogenous chemotactic stimulation; H2O2 release was more rapid, but the amount released was <40% of that mediated by Mac-1 adhesion; it was **inhibited** by anti-CD11a and anti-ICAM-1 antibodies; in contrast to that mediated by Mac-1, it was not **inhibited** by anti-CD11b antibody, neutrophil **inhibitory** factor (NIF), or cytochalasin B or H7. Thus, canine neutrophils seem to be able to utilize two members of the beta2 **integrin** family to interact with ICAM-1 and signal H2O2 production, with LFA-1 at an early stage without prior chemotactic stimulation and Mac-1 at a later stage requiring chemotactic stimulation.

L25 ANSWER 30 OF 67 MEDLINE on STN
ACCESSION NUMBER: 1999315182 MEDLINE
DOCUMENT NUMBER: 99315182 PubMed ID: 10387051
TITLE: Amino acid sequences within the alpha subunit of **integrin** alpha M beta 2 (Mac-1) critical for specific recognition of C3bi.
AUTHOR: Zhang L; Plow E F
CORPORATE SOURCE: Joseph J. Jacobs Center for Thrombosis and Vascular Biology, Department of Molecular Cardiology, The Cleveland Clinic Foundation, Ohio 44195, USA.
CONTRACT NUMBER: HL54921 (NHLBI)
SOURCE: BIOCHEMISTRY, (1999 Jun 22) 38 (25) 8064-71.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990730
Last Updated on STN: 19990730
Entered Medline: 19990722

AB Phagocytosis of opsonized particles by neutrophils and monocytes plays a

Search completed by David Schreiber 308-4292

[redacted]

central role in host defense mechanisms against foreign pathogens. This process depends on the interaction between C3bi, a degradation product derived from activation of the complement system, and the alpha M beta 2 (CD11b/CD18, Mac-1) receptor, the major **integrin** on neutrophils. Previous studies had established a central role for the I domain, a stretch of approximately 200 amino acids within the alpha M subunit in the binding of C3bi, as well as many other alpha M beta 2 ligands. The present study was undertaken to establish the molecular basis of C3bi recognition by alpha M beta 2. The strategy employed the use of a series of **mutant** receptors in which short segments of the I domain of alpha M were switched to the corresponding segments of alpha L, which is structurally very similar but does not bind C3bi. We report three major findings: (1) The C3bi binding pocket is composed of three regions, P147-R152, P201-K217, and K245-R261 of alpha M, which surround the cation binding site within the MIDAS motif of the I domain. (2) Within the latter segment, K245 plays a critical role in mediating C3bi binding to alpha M beta 2. Mutation of K245 to Ala significantly reduced C3bi binding but had no effect on binding of another alpha M beta 2 I domain ligand, NIF. (3) Blocking of C3bi binding to alpha M beta 2 by monoclonal antibodies is achieved through two different mechanisms: direct competition for the ligand binding site or induction of conformational changes. Overall, these studies support the hypothesis that many of the ligands of alpha M beta 2 bind to overlapping but not identical sites within the I domain. Although the same short structural segments within the I domain may be involved in binding, different amino acids within these segments may contact different ligands.

L25 ANSWER 31 OF 67 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999208706 MEDLINE
DOCUMENT NUMBER: 99208706 PubMed ID: 10191228
TITLE: The **hookworm platelet inhibitor** : functional blockade of **integrins GPIIb** /IIIa (alphaIIbbeta3) and **GPIa**/IIa (alpha2beta1) **inhibits platelet** aggregation and adhesion in vitro.
AUTHOR: **Chadderdon R C**; Cappello M
CORPORATE SOURCE: Dartmouth Medical School, Hanover, NH, USA.. robert.c.chadderdon@dartmouth.edu
CONTRACT NUMBER: AI-01299 (NIAID)
HD-27757 (NICHD)
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1999 May) 179 (5) 1235-41. Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990607

AB Hookworms, aggressive, blood-feeding, intestinal nematodes, are currently a leading cause of iron deficiency anemia in the developing world. An **inhibitor** of **platelet** aggregation and adhesion has been partially purified and characterized from soluble protein extracts of adult **Ancylostoma** caninum hookworms. This protein, named the **hookworm platelet inhibitor**, has an estimated molecular mass of 15 kDa as determined by size-exclusion chromatography. In addition to blocking **platelet** aggregation in response to a variety of agonists, the partially purified **inhibitor** also

prevents adhesion of resting **platelets** to immobilized fibrinogen and collagen. **Inhibitory** monoclonal antibodies were used to identify specific blockade of cell surface **integrins** **GPIIb**/IIIa (alphaIIbbeta3) and **GPIa**/IIa (alpha2beta1), the **platelet** receptors for fibrinogen and collagen, respectively. This broad-spectrum anti-**platelet** activity is also present in excretory and secretory products of adult worms, suggesting a biologic role for the **hookworm platelet** **inhibitor** in vivo.

L25 ANSWER 32 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:348251 SCISEARCH
THE GENUINE ARTICLE: 182AQ
TITLE: The **Hookworm Platelet** **Inhibitor** blocks fibrinogen binding to the **platelet integrin GPIIb**/IIIa (alpha(IIb)beta(3))
AUTHOR: **DelValle A (Reprint); Chadderdon R C;** Cappello M
CORPORATE SOURCE: YALE UNIV, SCH MED, DEPT PEDIAT, NEW HAVEN, CT 06510
COUNTRY OF AUTHOR: USA
SOURCE: PEDIATRIC RESEARCH, (APR 1999) Vol. 45, No. 4, Part 2, pp. 931-931.
Publisher: INT PEDIATRIC RESEARCH FOUNDATION, INC, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0031-3998.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L25 ANSWER 33 OF 67 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2000002883 MEDLINE
DOCUMENT NUMBER: 20002883 PubMed ID: 10531396
TITLE: Neutrophil **inhibitory** factor abrogates neutrophil adhesion by blockade of CD11a and CD11b beta(2) **integrins**.
AUTHOR: Lo S K; Rahman A; Xu N; Zhou M Y; Nagpala P; Jaffe H A; Malik A B
CORPORATE SOURCE: Department of Pharmacology, The University of Illinois College of Medicine, Chicago, Illinois 60612, USA.
CONTRACT NUMBER: HL 27016 (NHLBI)
HL 45638 (NHLBI)
HL 46350 (NHLBI)
SOURCE: MOLECULAR PHARMACOLOGY, (1999 Nov) 56 (5) 926-32.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124
AB We studied the basis of **inhibition** of polymorphonuclear leukocyte (PMN) adhesion induced by neutrophil **inhibitory** factor (NIF), a 41-kDa CD11/CD18 beta(2) **integrin**-binding protein isolated from the canine **hookworm** (**Ancylostoma** caninum). NIF blocked PMN adhesion in a concentration-dependent manner

Search completed by David Schreiber 308-4292

with complete blockade occurring at approximately 10 nM NIF. Because CD11a and CD11b beta(2) **integrins** are functionally active on stimulated PMNs, and yet NIF is postulated to **inhibit** only CD11b **integrin** by binding to its I domain, we evaluated the contributions of CD11a and CD11b beta(2) **integrins** in the mechanism of **inhibition** of PMN adhesion to endothelial cells. We observed an additive **inhibitory** effect (>90% **inhibition**) of PMN adhesion to endothelial cells when NIF was used in combination with anti-CD11b monoclonal antibodies, which alone at saturating concentrations reduced PMN adhesion by only 50%. NIF also prevented aggregation of phorbol ester-stimulated JY lymphoblastoid cells that expressed only the functionally active CD11a, suggesting that NIF also can **inhibit** CD11a-dependent response. We transduced the NIF cDNA into human dermal microvessel endothelial cells in which NIF synthesis and release prevented PMN adhesion to the transduced human dermal microvessel endothelial cells. These data indicated that the potent antiadhesive effect of NIF may be the result of **inhibition** of CD11a and CD11b beta(2) **integrins** on PMNs. Moreover, the strategy of NIF release from transduced endothelial cells suggests the feasibility of blocking the CD11a- and CD11b beta(2) **integrin** -dependent PMN adhesion and PMN migration responses specifically at sites of endothelial cell activation.

L25 ANSWER 34 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:477148 BIOSIS
DOCUMENT NUMBER: PREV199900477148
TITLE: Novel **inhibitors** of **platelet** function from bloodfeeding hookworms.
AUTHOR(S): **Del Valle, A. (1); Harrison, L. M.;** Cappello, M.
CORPORATE SOURCE: (1) Departments of Pediatrics and Epidemiology, Yale University School of Medicine, New Haven, CT USA
SOURCE: American Journal of Tropical Medicine and Hygiene, (Sept., 1999) Vol. 61, No. 3 SUPPL., pp. 175.
Meeting Info.: 48th Annual Meeting of the American Society of Tropical Medicine and Hygiene Washington, D.C., USA November 28-December 2, 1999 American Society of Tropical Medicine and Hygiene
. ISSN: 0002-9637.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 35 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:269953 BIOSIS
DOCUMENT NUMBER: PREV199900269953
TITLE: The **Hookworm Platelet Inhibitor** blocks fibrinogen binding to the **platelet integrin GPIIb**/IIIa (alphaIIbbeta3.
AUTHOR(S): **Del Valle, Antonio (1); Chadderdon, Robert C. (1);** Cappello, Michael (1)
CORPORATE SOURCE: (1) Dept. of Pediatrics, Yale University School of Medicine, New Haven, CT USA
SOURCE: Pediatric Research, (April, 1999) Vol. 45, No. 4 PART 2, pp. 160A.
Meeting Info.: Annual Meeting of the American Pediatric Society and the Society for Pediatric Research San Francisco, California, USA May 1-4, 1999
ISSN: 0031-3998.
DOCUMENT TYPE: Conference

Search completed by David Schreiber 308-4292

LANGUAGE: English

L25 ANSWER 36 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:241546 SCISEARCH
THE GENUINE ARTICLE: 178JH
TITLE: Invertebrate compounds acting on the hemostatic mechanism
AUTHOR: ArochaPinango C L (Reprint); Marchi R; Carvajal Z; Guerrero B
CORPORATE SOURCE: INST VENEZOLANO INVEST CIENT, CTR MED EXPT, APARTADO 21827, CARACAS 1020A, VENEZUELA (Reprint)
COUNTRY OF AUTHOR: VENEZUELA
SOURCE: BLOOD COAGULATION & FIBRINOLYSIS, (MAR 1999) Vol. 10, No. 2, pp. 43-68.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106.
ISSN: 0957-5235.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 228

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Physiological secretions from some invertebrates have toxic effects on mammalian blood coagulation and fibrinolytic systems. Some of these effects occur because the substances contained in the secretions resemble the components of the hemostatic system. Some of the substances have been characterized, and have been found to have similar molecular weights or sequences, which may indicate a common ancestry. The components can be divided into five groups: antithrombic agents (group I); **inhibitors** and activators of the prothrombinase complex (group II); substances that affect **platelet** function (group III); substances that affect the fibrinolytic mechanism (group IV); and a group of miscellaneous agents whose activities are difficult to group together (group V). In group I special mention of the antithrombin agents in Hirudo medicinalis should be made. In group II, the agents affecting the prothrombinase complex are antistasin from Haementeria officinalis, ghilanten from Haementeria Ghiliani and the tick anticoagulant protein from Ornithodoros moubata, a factor V activator/**inhibitor** from Lonomia achelous and factor II and factor X activators from L. achelous and Lonomia obliqua. Examples of factors which affect **platelet** function (group III) are glossina from the black fly Glossina morsitans, calin from H. medicinalis, decorsin (a desintegrin) from Macrobdella decorsa, and FAGA from Stichopus japonicus selenka. The first three of these are **inhibitors** of **platelet** aggregation, and the last is an inducer. The plasminogen activators (group IV) from the L. achelous caterpillar and Entriatoma maculata trigger the fibrinolytic system, whereas hementin from H. officinalis and hementerin from Haementeria depressa are directly fibrinolytic. The last group of substances (group V) include those with factor-XIIa-like activity from D. farinae, kallikrein-like activity and a factor XIII degrading enzyme from L. achelous, destabilase from H. medicinalis and prolixin S (nitroforin 2, or anti-factor-IXa) from Rhodnius prolixus. Some of these components have been well characterized, cloned and prepared in **recombinant** form, and seem to be very promising from the therapeutic point of view. (C) 1999 Lippincoa Williams & Wilkins.

L25 ANSWER 37 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:282362 HCAPLUS
DOCUMENT NUMBER: 129:3851
TITLE: Method of detecting neutrophil **inhibitory**

Search completed by David Schreiber 308-4292

factor mimics
INVENTOR(S): Moyle, Matthew; Foster, David L.; Vlasuk, George P.
PATENT ASSIGNEE(S): Corvas International, Inc., USA
SOURCE: U.S., 134 pp., Cont.-in-part of U.S. Ser. No. 151,064.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5747296	A	19980505	US 1993-173510	19931223
US 5708141	A	19980113	US 1994-249041	19940524
US 5919900	A	19990706	US 1995-450497	19950526
US 5789178	A	19980804	US 1995-458218	19950602

PRIORITY APPLN. INFO.: US 1992-881721 B2 19920511
US 1992-996972 A2 19921224
US 1993-60433 A2 19930511
US 1993-151064 A2 19931110
US 1993-173510 A3 19931223

AB Compns. enriched for neutrophil **inhibitory** factor which **inhibit** neutrophil activity including adhesion to vascular endothelial cells are provided. Also provided are **recombinant** neutrophil **inhibitory** factors which also **inhibit** neutrophil activity. Such compns. may comprise a glycoprotein isolated from nematodes. These compns. and **recombinant** neutrophil **inhibitory** factors are useful in the therapy of conditions which involve abnormal or undesired inflammatory responses.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 38 OF 67 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1998282278 MEDLINE
DOCUMENT NUMBER: 98282278 PubMed ID: 9616214
TITLE: In vivo expression of neutrophil **inhibitory** factor via gene transfer prevents lipopolysaccharide-induced lung neutrophil infiltration and injury by a beta2 **integrin**-dependent mechanism.
AUTHOR: Zhou M Y; Lo S K; Bergenfeldt M; Tiruppathi C; Jaffe A; Xu N; Malik A B
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, The University of Illinois, Chicago, Illinois 60612, USA.
CONTRACT NUMBER: HL-27016 (NHLBI)
HL-45638 (NHLBI)
HL-46350 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1998 Jun 1) 101 (11) 2427-37.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980626

AB The binding of beta2 (CD18) **integrins** on PMN cell membrane to intercellular adhesion molecule (ICAM) counter-receptors on the surface of

[redacted]

vascular endothelial cells mediates PMN adhesion to endothelial cells. Neutrophil **inhibitory** factor (NIF), a 41-kD glycoprotein isolated from the canine **hookworm** (**Ancylostoma** caninum), is a beta2 **integrin** antagonist that **inhibits** PMN adhesion tc endothelial cells. We transferred the NIF gene into CD1 mouse lungs by intravenous injection of cationic liposomes to study the effects of in vivo NIF expression on LPS-induced lung PMN sequestration and the development of lung injury. RT-PCR and Northern blot analysis indicated the lung-selective expression of the NIF transgene, and immunocytochemistry showed prominent NIF expression in pulmonary microvessel endothelial cells. NIF staining was also observed in intraluminal leukocytes present in pulmonary microvessels. This may be the result of NIF binding to leukocytes after its secretion from the transduced lung cells, since there was no evidence of NIF gene expression in circulating leukocytes. Pulmonary vascular NIF expression abrogated the lung tissue PMN uptake and airspace migration of PMN and prevented lung vascular injury (as measured by the lung tissue uptake of [125I]labeled albumin) after the intraperitoneal LPS challenge (200 microg/mouse). Expression of a control protein, chloramphenicol acetyltransferase (CAT), by the same strategy, had no effect on these responses. In vitro studies showed that NIF prevented mouse PMN adhesion consistent with the **inhibition** of lung uptake after LPS challenge in NIF transgene-expressing mice. We conclude that pulmonary vascular expression of NIF, a specific beta2 **integrin**- binding protein, is a potentially useful gene transfer strategy in modulating the infiltration of PMN across the alveolar-capillary epithelial barrier and in preventing lung vascular endothelial injury.

L25 ANSWER 39 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1998:377748 SCISEARCH
THE GENUINE ARTICLE: ZM870
TITLE: Neutrophil **inhibitory** factor treatment of focal cerebral iscnemia in the rat
AUTHOR: Jiang N; Chopp M (Reprint); Chahwala S
CORPORATE SOURCE: HENRY FORD HOSP, DEPT NEUROL, 2799 W GRAND BLVD, DETROIT, MI 48202 (Reprint); HENRY FORD HLTH SCI CTR, DEPT NEUROL, DETROIT, MI 48202; OAKLAND UNIV, DEPT PHYS, ROCHESTER, MI 48309; PFIZER LTD, CENT RES, SANDWICH CT13 9NJ, KENT, ENGLAND
COUNTRY OF AUTHOR: USA; ENGLAND
SOURCE: BRAIN RESEARCH, (30 MAR 1998) Vol. 788, No. 1-2, pp. 25-34

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0006-8993.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 70

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The present study was designed to determine whether a **hookworm** -derived **recombinant** neutrophil **inhibitory** factor (rNIF) is neuroprotective when administered after initiation of focal cerebral ischemia in the rat. We measured the rNIF dose-response on cerebral infarct volume, the therapeutic time window, the therapeutic response to permanent ischemia, and whether rNIF treatment delays the maturation of the ischemic lesion (2 days), or reduces cerebral infarct volume at 7 days after middle cerebral artery occlusion (MCAO). MCAO was induced by an insertion of intraluminal 4-0 monofilament nylon suture into

internal carotid artery (n = 195). We demonstrate a significant neuroprotective effect of rNIF administration 48 h after MCAO in a dose-dependent fashion when treatment was initiated upon reperfusion after 2 h MCAO and maintained until 48 h after MCAO. The beneficial effect was lost under conditions of permanent MCAO. The therapeutic time window is 4 h after MCAO. Brief treatment (6 h) is not sufficient to provide protection for the final ischemic damage. Continuous treatment with a high dose of rNIF for a long duration (7 days) is necessary to achieve maximum neuroprotection. (C) 1996 Elsevier Science B.V.

L25 ANSWER 40 OF 67 MEDLINE on STN
ACCESSION NUMBER: 97362245 MEDLINE
DOCUMENT NUMBER: 97362245 PubMed ID: 9211902
TITLE: Identification and reconstruction of the binding site within alphaMbeta2 for a specific and high affinity ligand, NIF.
AUTHOR: Zhang L; Plow E F
CORPORATE SOURCE: Joseph J. Jacobs Center for Thrombosis and Vascular Biology, Department of Molecular Cardiology, The Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jul 11) 272 (28) 17558-64.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970825
Last Updated on STN: 19970825
Entered Medline: 19970814

AB Engagement of the alphaMbeta2 (CD11b/CD18, Mac-1) **integrin** on neutrophils supports adhesion and induces various cellular responses. These responses can be blocked by a specific ligand of alphaMbeta2, neutrophil **inhibitory** factor (NIF). The molecular basis of alphaMbeta2-NIF interactions was studied. The single chain alphaM subunit, expressed on the surface of human 293 cells, bound NIF with an affinity equivalent to that of alphaMbeta2 heterodimer. This observation, coupled with previous data showing that the alphaMI domain alone supported high affinity NIF binding, indicated that the binding site for NIF is restricted to the I domain. Guided by the crystal structure of the alphaMI domain, 16 segments corresponding to the entire outer hydrated surface of alphaMI domain were switched to their counterparts sequences in alphaL, which does not bind NIF. Surface expression and heterodimer formation were achieved for all **mutants**, and correct folding was confirmed. Of the 16 switches, only 5 affected NIF binding substantially, reducing affinity by 8-300-fold. These data confined the NIF-binding site to a narrow region composed of Pro147-Arg152, Pro201-Lys217, and Asp248-Arg261 of alphaM. Verifying this localization, when these segments were introduced into the alphaXI-domain, the resulting chimeric receptor was converted into a high affinity NIF-binding protein.

L25 ANSWER 41 OF 67 MEDLINE on STN
ACCESSION NUMBER: 97387259 MEDLINE
DOCUMENT NUMBER: 97387259 PubMed ID: 9243305
TITLE: A peptide derived from neutrophil **inhibitory** factor (NIF) blocks neutrophil adherence to endothelial cells.
AUTHOR: Madden K; Janczak J; McEnroe G; Lim D; Hartman T; Liu D;

Stanton L
CORPORATE SOURCE: Scios Inc., Sunnyvale, CA 94086, USA.
CONTRACT NUMBER: 1 R43 HL55028-01 (NHLBI)
SOURCE: INFLAMMATION RESEARCH, (1997 Jun) 46 (6) 216-23.
Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 19970916
Entered Medline: 19970904

AB OBJECTIVE AND DESIGN: Peptides derived from neutrophil **inhibitory** factor (NIF), a known antagonist of Mac-1, were evaluated as **inhibitors** of neutrophil adherence. MATERIAL: In vitro assays of adherence employed: 1) human polymorphonuclear cells (PMN), 2) human umbilical vein endothelial cells (HUVEC), and 3) CHO cells expressing ICAM-1 (CHO-ICAM cells). TREATMENT: Cells, pretreated with NIF-derived peptides (0.1-100 microM) for 10 minutes, were permitted to adhere for 20 min in the continued presence of peptide. METHODS: Cell-based assays: 1) PMN adherence to HUVEC, 2) PMN adhesion to immobilized human serum proteins, and 3) adherence of CHO-ICAM cells to immobilized Mac-1. RESULTS: A NIF-derived peptide of 29 amino acids blocked PMN adherence to HUVEC, but behaved somewhat differently than the parent NIF protein. NIF specifically antagonized Mac-1 dependent adherence, but the peptide blocked neutrophil adherence that was dependent upon both Mac-1 and LFA-1 **integrins**. CHO-ICAM adherence to Mac-1 was blocked by NIF, but not by the peptide. Binding studies with NIF and the peptide indicate that the molecules bind to different sites. CONCLUSIONS: A peptide derived from NIF blocks PMN adherence but, unlike NIF, the mechanism of action is not mediated by direct antagonism Mac-1.

L25 ANSWER 42 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1997:286029 HCAPLUS
DOCUMENT NUMBER: 127:4050
TITLE: Polymorphonuclear leukocyte (PMN) **inhibitory** factor prevents PMN-dependent endothelial cell injury by an anti-adhesive mechanism
AUTHOR(S): Ohno, Shoji; Malik, Asrar B.
CORPORATE SOURCE: Rush-Presbyterian-St. Luke's Medical Center, Department of Pharmacology, Chicago, IL, USA
SOURCE: Journal of Cellular Physiology (1997), 171(2), 212-216
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Neutrophil **inhibitory** factor (NIF), a 41-kD glycoprotein isolated from the canine **hookworm, inhibits** CD11b/CD18-dependent neutrophil adhesion by binding to CD11b. We studied the effects of NIF on neutrophil-dependent endothelial cell injury using bovine pulmonary microvessel endothelial cells grown on microporous filters. Endothelial injury was detd. as an increase in the transendothelial 125I-albumin clearance rate (a measure of transendothelial permeability). Layering of neutrophils on the endothelial cell monolayer (ratio of 10 neutrophils: 1 endothelial cell) followed by activation of neutrophils with 500 nM of phorbol 12-myristate 13-acetate (PMA) increased transendothelial permeability of albumin by 3- to 4-fold over control monolayers. Pretreatment of neutrophils with NIF

at concns. of 100 nM and above prevented the increased permeability. Pretreatment of neutrophils with the anti-CD18 monoclonal antibody (mAb) IB4 similarly prevented the increase of permeability. Pretreatment of neutrophils with OKM-1, a control isotype-matched mAb directed against an irrelevant epitope on CD11b mAb, did not affect the neutrophil-dependent increase in permeability. NIF reduced the adhesion of neutrophils at concns. of .gtoreq. 100 nM and this effect was abolished by an anti-NIF polyclonal Ab. However, NIF did not prevent the generation of superoxide anions following PMA-induced activation of neutrophils layered on endothelial cell. These findings indicate that NIF **inhibits** the neutrophil-dependent endothelial injury by preventing CD11b/CD18-mediated neutrophil adhesion, but without altering the oxidant generating capacity of neutrophils interacting with the endothelial cell monolayer.

L25 ANSWER 43 OF 67 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 97:795907 SCISEARCH
THE GENUINE ARTICLE: YC301
TITLE: Antithrombotic efficacy of a **recombinant** nematode anticoagulant peptide (rNAP5) in canine models of thrombosis after single subcutaneous administration
AUTHOR: Rebello S S; Blank H S; Rote W E; Vlasuk G P; Lucchesi B R (Reprint)
CORPORATE SOURCE: UNIV MICHIGAN, SCH MED, DEPT PHARMACOL, 1301C MED SCI RES BLDG 3, ANN ARBOR, MI 48109 (Reprint); UNIV MICHIGAN, SCH MED, DEPT PHARMACOL, ANN ARBOR, MI 48109
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (OCT 1997) Vol. 283, No. 1, pp. 91-99.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0022-3565.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We describe the antithrombotic effects of **recombinant** nematode anticoagulant peptide (rNAP5), a selective and direct factor Xa **inhibitor**, after a single s.c. administration in canine models of arterial and venous thrombosis. The systemic anticoagulant effects of rNAP5 were evaluated initially in conscious dogs after s.c. dosing (0.03, 0.1 and 0.3 mg/kg) that resulted in a dose-dependent increase in the activated clotting time and the activated partial thromboplastin time. The antithrombotic effects of rNAP5 were evaluated in anesthetized dogs where saline or rNAP5 (0.03, 0.1 and 0.3 mg/kg s.c.) was administered 1 hr before the left circumflex coronary artery was subjected to electrolytic injury. In the saline group (n = 10), the left circumflex artery occluded in 79 +/- 9 min, and 5 of 10 animals progressed to sudden death due to ventricular fibrillation. rNAP5 significantly prolonged the time to occlusion in the 0.03 mg/kg (163 +/- 62 min) and 0.1 mg/kg (327 +/- 62) treatment groups (n = 6). In the 0.3 mg/kg group (n = 5), all of the injured vessels remained patent for 8 hr. There was a dose-dependent reduction in the thrombus mass in the rNAP5-treated animals as compared with controls, as well as a lower mortality rate. rNAP5, in the doses of 0.03 and 0.1 mg/kg, did not alter the bleeding time, whereas 0.3 mg/kg produced a 5-fold increase. In a separate study, we evaluated the efficacy of rNAP5 (0.1 mg/kg) in the prevention of carotid artery and jugular vein thrombosis. In response to endothelial injury, the carotid artery and jugular vein in the saline group (n = 6) occluded in 142 +/- 16 and 100

+/- 11 min, respectively, compared with rNAP5, which maintained vessel patency in the carotid artery (6/6) and jugular vein (5/6) and significantly decreased the thrombus weights. The results demonstrate that rNAP5 has antithrombotic efficacy in canine models of arterial and venous thrombosis after a single s.c. administration.

L25 ANSWER 44 OF 67 MEDLINE on STN
ACCESSION NUMBER: 97094706 MEDLINE
DOCUMENT NUMBER: 97094706 PubMed ID: 8939940
TITLE: A discrete site modulates activation of I domains. Application to **integrin** alphaMbeta2.
AUTHOR: Zhang L; Plow E F
CORPORATE SOURCE: Joseph J. Jacobs Center for Thrombosis and Vascular Biology, Department of Molecular Cardiology, The Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA..
ZHANGL@CESMTP.CCF.ORG
CONTRACT NUMBER: HL38292 (NHLBI)
HL43721 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Nov 22) 271 (47) 29953-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970113

AB A central characteristic of **integrin** adhesion receptors is their capacity to become activated, thereby enhancing their affinity for ligands. Here, we report the identification of a discrete site within the I domain of **integrin** alphaMbeta2, which modulates the adhesive activity of this receptor. Based upon the crystal structure, this region is composed of two short and spatially proximal loops, E162QLKKSKTL and Q190NNPNPRS. Mutations in these loops yield receptors which support spontaneous cell adhesion to fibrinogen, whereas mutation of an adjacent region and wild-type receptors require activation to adhere to this substrate. An activating monoclonal antibody enhanced the adhesive activity of one but not the other loop **mutants**, suggesting that the activation states of these two **mutant** receptors were not identical. Given that similar I domains exist in several other **integrin** alpha subunits and non-**integrin** proteins, and possibly in all **integrin** beta subunits, these two loop segments may represent a universal target for controlling **integrin** activation and the function of other I domain-containing proteins. In support of this hypothesis, several naturally occurring mutations that activate von Willebrand factor map to the same loops of its I(A) domain.

L25 ANSWER 45 OF 67 MEDLINE on STN
ACCESSION NUMBER: 96279375 MEDLINE
DOCUMENT NUMBER: 96279375 PubMed ID: 8663418
TITLE: Overlapping, but not identical, sites are involved in the recognition of C3bi, neutrophil **inhibitory** factor, and adhesive ligands by the alphaMbeta2 **integrin**.
AUTHOR: Zhang L; Plow E F
CORPORATE SOURCE: Joseph J. Jacobs Center for Thrombosis and Vascular Biology, Department of Molecular Cardiology, The Cleveland

Search completed by David Schreiber 308-4292

[redacted]

Clinic Foundation, Cleveland, Ohio 44195, USA.
CONTRACT NUMBER: HL38292 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jul 26) 271 (30) 18211-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960903

AB The alphaMbeta2 (CD11b/CD18, Mac-1) **integrin** receptor binds numerous ligands, including neutrophil **inhibitory** factor (NIF), C3bi, and certain immobilized protein substrates, represented by denatured ovalbumin. These ligands share no obvious structural similarities, yet their interactions with receptor are **inhibited** by NIF and involve the I domain, a stretch of approximately 200 amino acids in the alphaM subunit. **Recombinant** wild-type and **mutant** forms of alphaMbeta2 have been used to compare the recognition requirements of these ligands. The various constructs were expressed efficiently on the surface of human embryonic kidney 293 cells and formed alpha.beta heterodimeric complexes. The wild-type transfectants bound the three ligands in a similar fashion to naturally occurring alphaMbeta2. NIF **inhibited** these interactions, and deletion of the D248PLGY from within the I domain abolished binding of all three ligands, suggesting an overlapping recognition specificity. A single point mutation of Ser138 to Ala in the beta2 subunit abolished C3bi binding and cell adhesion but did not affect NIF binding. A switch of the R281QELNTI sequence in helix 6 of the alphaM I domain to the corresponding sequence in the I domain of the alphaL (QETLHKF) subunit completely abrogated adhesion while not affecting C3bi and NIF binding. The two **mutant** receptors also did not support activation-dependent adhesion to fibrinogen. Thus, the contact sites for NIF, C3bi, and adhesive proteins, represented by denatured ovalbumin and fibrinogen, in alphaMbeta2 are overlapping but not identical.

L25 ANSWER 46 OF 67 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER: 96279118 MEDLINE
DOCUMENT NUMBER: 96279118 PubMed ID: 8663417
TITLE: Solvent-accessible residues on the metal ion-dependent adhesion site face of **integrin** CR3 mediate its binding to the neutrophil **inhibitory** factor.
AUTHOR: Rieu P; Sugimori T; Griffith D L; Arnaout M A
CORPORATE SOURCE: Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jul 5) 271 (27) 15858-61.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960911
Last Updated on STN: 19970203
Entered Medline: 19960829

Search completed by David Schreiber 308-4292

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AB Neutrophil adhesion-dependent functions such as chemotaxis, spreading, and phagocytosis are **inhibited** by neutrophil **inhibitory** factor (NIF), a glycoprotein produced by the **hookworm** **Ancylostoma** caninum. The NIF binding site has been localized to the A-domain of **integrin** CR3 (CD11b/CD18) and shown to be metal-dependent. The recently solved crystal structure of the A-domain from CD11b revealed a putative metal ion-dependent adhesion site (MIDAS) on the top of the structure. To determine if NIF binds to the A-domain at its MIDAS face, amino acid substitutions involving 24 residues present in surface loops and adjacent helices in the structure were created. The expressed CD11b A-domain and CR3 heterodimers were then tested in a blinded manner for their ability to bind to biotinylated NIF. The solvent-exposed Gly143, Asp149, Glu178-Glu179, and Arg208, all located on the MIDAS face, in close proximity to the metal ion, were involved in CR3-NIF interaction. These data show that the natural **integrin** antagonist, NIF, binds to CR3 through the MIDAS region and identify putative contact residues in this region that could be targeted therapeutically.

L25 ANSWER 47 OF 67 MEDLINE on STN
ACCESSION NUMBER: 97011756 MEDLINE
DOCUMENT NUMBER: 97011756 PubMed ID: 8858748
TITLE: Attenuation of the inflammatory response in an animal colitis model by neutrophil **inhibitory** factor, a novel beta 2-**integrin** antagonist.
AUTHOR: Meenan J; Hommes D W; Mevissen M; Dijkhuizen S; Soule H; Moyle M; Buller H R; ten Kate F W; Tytgat G N; van Deventer S J
CORPORATE SOURCE: Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands.
SOURCE: SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY, (1996 Aug) 31 (8) 786-91.
Journal code: 0060105. ISSN: 0036-5521.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961230

AB BACKGROUND: Neutrophils are significant effector cells in acute inflammatory bowel disease. Recruitment of these cells is dependent on beta 2-**integrin**-mediated adhesion and transmigration. The efficacy of neutrophil **inhibitory** factor (NIF), an antagonist of the beta 2-**integrin** CD11b/CD18, in ameliorating inflammation was tested in an animal model of acute colitis. METHOD: Immune-complex colitis was induced in groups of rabbits by using various formalin concentrations (2%, 0.75%, and 0.5%). Animals were treated with rNIF, 10 mg/kg. After they had been killed the mucosal appearance was scored, and tissue saved for histology and quantitation of myeloperoxidase (MPO), leukotriene B4 (LTB4), prostaglandin E2 (PGE2), and thromboxane B2 (TXB2). RESULTS: In the 2% formalin group therapy with rNIF resulted in lower LTB4 ($p < 0.05$) levels. For the 0.75% and 0.5% groups, MPO was lower with rNIF treatment ($p < 0.03$ and $p < 0.05$, respectively), as were LTB4 concentrations (both, $p < 0.04$). PGE2 and TXB2 levels remained unchanged. Histology showed polymorphonuclear cell infiltration to be reduced by rNIF in the 2% and 0.75% formalin-treatment groups ($p < 0.05$). CONCLUSION: These results suggest that blockade of CD11b/CD18-mediated mucosal

Search completed by David Schreiber 308-4292

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neutrophil recruitment may form part of a strategy for targeted therapeutic intervention in inflammatory bowel disease.

L25 ANSWER 48 OF 67 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 96188775 MEDLINE
DOCUMENT NUMBER: 96188775 PubMed ID: 8603998
TITLE: The role of CD11/CD18 **integrins** in the reverse passive Arthus reaction in rat dermal tissue.
AUTHOR: Rote W E; Dempsey E; Maki S; Vlasuk G P; Moyle M
CORPORATE SOURCE: Department of Molecular Pharmacology, Corvas International, Inc., San Diego, CA 92121, USA.
SOURCE: JOURNAL OF LEUKOCYTE BIOLOGY, (1996 Feb) 59 (2) 254-61. Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960524
Last Updated on STN: 19960524
Entered Medline: 19960515

AB The CD11/CD18 leukocyte **integrins** are necessary for tissue localization of neutrophils, an early requisite event in inflammation. We have analyzed the contribution of CD11a/CD18 and CD11b/CD18 to local neutrophil accumulation and tissue injury in the reverse passive Arthus reaction in the rat dermis. Experimental groups comprised animals that received an intravenous infusion of (1) **recombinant** neutrophil **inhibitory** factor (NIF), a **hookworm**-derived antagonist of CD11b/CD18; (2) monoclonal antibody to CD11a/CD18 (TA-3); (3) a combination of these agents; (4) a monoclonal antibody to CD18 (WT.3); or (5) saline. Administration of **recombinant** NIF or anti-CD11a/CD18 monoclonal antibody alone produced a slight reduction in neutrophil accumulation but did not affect edema formation. In contrast, a combination of these antagonists yielded a significant reduction in neutrophil accumulation and a modest reduction in edema, equivalent to levels observed with either anti-CD18 antibodies or animals that were rendered neutropenic. These results indicate that neutrophil infiltration in rat dermal tissue in the reverse passive Arthus reaction is dependent predominantly on the leukocyte **integrins** CD11a/CD18 and CD11b/CD18 and that either of these **integrins** is sufficient for neutrophil trafficking in this inflammatory setting.

L25 ANSWER 49 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:466174 HCAPLUS
DOCUMENT NUMBER: 125:185231
TITLE: Protective effects of neutrophil **inhibitory** factor (NIF) on neutrophil dependent endothelial cell injury
AUTHOR(S): Ohno, Shoji; Kitamura, Satoshi
CORPORATE SOURCE: Dep. Pulmonary Med., Jichi Med. Sch., Tochigi, 329-04, Japan
SOURCE: Ensho (1996), 16(4), 249-253
CODEN: ENSHEE; ISSN: 0389-4290
PUBLISHER: Nippon Ensho Gakkai Jimukyoku
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB NIF is a novel 41 kDa glycoprotein from canine **hookworm** and potently **inhibits** CD 11/CD 18-dependent neutrophil adhesion in vitro, by binding to CD 11 b/CD 18. We examd. the effects of NIF on

Search completed by David Schreiber 308-4292

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neutrophil-dependent endothelial cell injury. Studies were made in bovine pulmonary microvessel endothelial monolayer and the injury was estd. as an increase of transendothelial 125I-albumin permeability. Layering of neutrophils onto monolayer followed by activation of neutrophils with 500 nM of phorbol 12-myristate 13-acetate (PMA) increased the permeability (by 3-4 folds over control that is monolayers). Pretreatment of neutrophils with NIF completely protected the increase of permeability in a dose-dependent manner at 100 nM and above. Neutrophils pretreated with monoclonal antibody (mAb)IB 4, an anti-CD 18 mAb, also prevented the increase of permeability. In contrast, pretreatment of neutrophil with OKM-1, a control anti-CD 11b mAb, did not affect the neutrophil-dependent permeability increase. We conclude that NIF protects the neutrophil-dependent endothelial cell injury by preventing CD 18 dependent neutrophil activation.

L25 ANSWER 50 OF 67 MEDLINE on STN
ACCESSION NUMBER: 96246357 MEDLINE
DOCUMENT NUMBER: 96246357 PubMed ID: 8801197
TITLE: Mechanisms underlying neutrophil adhesion to apical epithelial membranes.
AUTHOR: Meenan J; Mevissen M; Monajemi H; Radema S A; Soule H R; Moyle M; Tytgat G N; van Deventer S J
CORPORATE SOURCE: Department of Haemostasis, Inflammation, Atherosclerosis and Thrombosis (HIAT) Research, Academic Medical Centre, University of Amsterdam, Netherlands.
SOURCE: GUT, (1996 Feb) 38 (2) 201-5.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961015
Last Updated on STN: 19970203
Entered Medline: 19961001

AB Crypt abscesses allow prolonged apposition of activated neutrophils to the epithelial surface of the colon. Adhesion of neutrophils to both the vascular endothelium and basolateral epithelial membrane share common effector molecules but are distinct processes. This study aimed to define the mechanisms that effect adhesion, independent of transmigration, to the apical epithelium. HT29 (cl 19A) cells were grown to confluency and incubated with neutrophils under conditions of: (i) neutrophil stimulation with phorbol-myristate-acetate; (ii) monolayer stimulation with interferon gamma, tumour necrosis factor alpha (IFN gamma, TNF alpha); and (iii) recent epithelial cell trypsinisation. These experiments were carried out in the presence of neutralising antibodies to CD18, CD11b, LFA-1, E-selectin, P-selectin, intracellular adhesion molecule 1 (ICAM-1), and ICAM-2; a novel CD11b/CD18 antagonist, neutrophil **inhibitory** factor (rNIF); adenosine receptor agonists (5'N-ethycarboxamido adenosine/N6-cylopentyladenosine (NECA/CPA)) and a **platelet** activating factor (PAF) receptor antagonist lexipafant. Adhesion of stimulated neutrophils to resting monolayers was Mac-1, CD18 dependent and ICAM-1, ICAM-2, E-selectin, P-selectin, PAF independent. Cytokine activated monolayers exhibited higher binding of neutrophils which was **inhibited** by rNIF and aCD18. Recently trypsinised monolayers bound neutrophils in a CD11b/CD18 and CD18 independent manner. Adenosine agonists failed to influence neutrophil adhesion under any condition. This study shows neutrophil adhesion to apical epithelial membranes is similar to that at the epithelial basolateral membrane, though different

to that seen at the vascular endothelium. These results highlight regional differences in neutrophil adhesion molecule usage.

L25 ANSWER 51 OF 67 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 96155208 MEDLINE
DOCUMENT NUMBER: 96155208 PubMed ID: 8587805
TITLE: The anti-haemostatic strategies of the human **hookworm Necator** americanus.
AUTHOR: Furmidge B A; Horn L A; Pritchard D I
CORPORATE SOURCE: Department of Life Science, University of Nottingham.
SOURCE: PARASITOLOGY, (1996 Jan) 112 (Pt 1) 81-7.
Journal code: 0401121. ISSN: 0031-1820.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960404
Last Updated on STN: 19960404
Entered Medline: 19960325

AB The human **hookworm Necator** americanus appears to have evolved a number of complementary strategies to overcome the host's haemostatic processes. These include the **inhibition** of blood coagulation, **platelet** aggregation and mediator release, and the secretion of fibrinogenolytic enzymes. These strategies presumably allow the parasite to establish the chronic infections so often documented in human populations.

L25 ANSWER 52 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:690153 HCAPLUS
DOCUMENT NUMBER: 123:74905
TITLE: Antihemostatic agents from **Necator** americanus
INVENTOR(S): Pritchard, David Idris
PATENT ASSIGNEE(S): University of Nottingham, UK
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9512615	A1	19950511	WO 1994-GB2406	19941102

W: CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: GB 1993-22576 19931102

AB Excretory-secretory (ES) products of the human **hookworm**, **N. americanus**, are useful as antihemostatic agents. In particular, the products **inhibit** the activity of coagulation factor Xa and **inhibit platelet** aggregation. Thus, adult **N. americanus** were isolated from hamsters, washed, and cultured in RPMI 1640 medium, and the supernatant was concd. by centrifugation. The concd. ES products prolonged the clotting time of **platelet**-poor citrated plasma in the prothrombin time test, activated partial thromboplastin test, and Stypven clotting time test, **inhibited** factor Xa activity on cleavage of a fluorogenic synthetic oligopeptide substrate, and degraded human fibrinogen.

Search completed by David Schreiber 308-4292

L25 ANSWER 53 OF 67 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 96062307 MEDLINE
DOCUMENT NUMBER: 96062307 PubMed ID: 7594491
TITLE: Neutrophil **inhibitory** factor prevents neutrophil-dependent lung injury.
AUTHOR: Barnard J W; Biro M G; Lo S K; Ohno S; Carozza M A; Moyle M; Soule H R; Malik A B
CORPORATE SOURCE: Department of Pharmacology, Rush Presbyterian-St. Luke's Medical Center, Chicago, IL 60612, USA.
CONTRACT NUMBER: HL22016 (NHLBI)
HL46350 (NHLBI)
HL49883 (NHLBI)
+
SOURCE: JOURNAL OF IMMUNOLOGY, (1995 Nov 15) 155 (10) 4876-81.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951218

AB Neutrophil **inhibitory** factor (NIF) is a recently cloned 41-kDa protein from the canine **hookworm** that binds CD11b/CD18 and **inhibits** CD11b/CD18-dependent neutrophil adhesion. We evaluated NIF's effects on neutrophil-dependent lung injury in guinea pigs. Pulmonary vascular endothelial CD54 (ICAM-1) was induced in buffer-perfused lungs by 90-min exposure to 1000 U/ml TNF-alpha. Human neutrophils (2 x 10(7)) were added to the perfusate and activated by 5 x 10(-9) PMA; in some lungs, the neutrophils were pretreated with NIF (100 nM) before their addition to the perfusate. Lung injury was assessed by wet:dry weight ratio, and neutrophil uptake by lung myeloperoxidase (MPO) activity. HUVEC exposed to TNF-alpha for 90 min were assayed for neutrophil adhesion, and we compared PMA-stimulated neutrophil adhesion to endothelial cells and fibrinogen-coated plates. PMA-induced pulmonary edema (lung wet:dry ratio increased from 8.8 +/- 0.7 to 18.8 +/- 4.4) was **inhibited** by NIF (10.0 +/- 1.0). Lung MPO activity concomitantly decreased from 17.1 +/- 6.1 to 8.7 +/- 1.8 U/mg dry lung tissue in the NIF-treated group, similar to controls (6.9 +/- 2.0). Endothelial monolayer experiments confirmed that NIF reduced neutrophil adherence (basal adhesion of 11 +/- 3% increased to 30 +/- 5% with TNF-alpha pretreatment of endothelial cells, an increase that was reduced to 10 +/- 4% with NIF). Moreover, NIF prevented PMA-induced neutrophil adhesion to fibrinogen, a CD11b/CD18-dependent event, but produced a smaller decrease in adherence to endothelial cells, which also involves CD11a/CD18 **integrins**. These studies indicate that NIF prevents neutrophil-dependent lung vascular injury by **inhibiting** neutrophil adhesion to the TNF-alpha-activated endothelium.

L25 ANSWER 54 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:33807 HCAPLUS
DOCUMENT NUMBER: 122:1077
TITLE: Novel neutrophil **inhibitors** for use as inflammation **inhibitors**
INVENTOR(S): Moyle, Matthew; Foster, David Lee; Vlasuk, George Phillip
PATENT ASSIGNEE(S): Corvas International, Inc., USA

Search completed by David Schreiber 308-4292

[redacted]

SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9414973	A1	19940707	WO 1993-US12626	19931223
W: AU, CA, FI, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2152599	AA	19940707	CA 1993-2152599	19931223
AU 9460805	A1	19940719	AU 1994-60805	19931223
AU 694103	B2	19980716		
EP 682714	A1	19951122	EP 1994-907114	19931223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08505055	T2	19960604	JP 1993-515483	19931223

PRIORITY APPLN. INFO.: US 1992-996972 A 19921224
US 1993-60433 A 19930511
US 1993-151064 A 19931110
WO 1993-US12626 W 19931223

AB Peptides that **inhibit** neutrophil activity including adhesion to vascular endothelial cells are described for use as anti-inflammatories with a greater specificity than prior art inflammation **inhibitors** . The peptides are derived from a glycoprotein of **hookworm** and may be manufd. by expression of the corresponding gene. Neutrophil **inhibitors** were purified 200-fold (12% yield) from lysates of canine **hookworm** by chromatog. on ConA-Sepharose, Superdex 200, ceramic hydroxyapatite and by reverse phase HPLC, or by a combination of ion-exchange chromatog., SDS-polyacrylamide gel electrophoresis, and isoelec. focussing. A cDNA was cloned by std. methods using amino acid sequence-derived primers to obtain a partial cDNA by PCR and the full-length cDNA expressed in COS-7 and CHO cells and in Pichia pastoris. The protein did not affect **ADP**-induced **platelet** aggregation. The primary receptor for the **inhibitor** was the CD11b/CD18. The neutrophil **inhibitor** was shown to have a protective effect on arachidonic acid-induced neutrophil infiltration into ear tissue in a rat model..

L25 ANSWER 55 OF 67 MEDLINE on STN DUPLICATE 16

ACCESSION NUMBER: 95014481 MEDLINE
DOCUMENT NUMBER: 95014481 PubMed ID: 7929363
TITLE: Functional interaction between the **integrin** antagonist neutrophil **inhibitory** factor and the I domain of CD11b/CD18.
COMMENT: Erratum in: J Biol Chem 1995 Mar 17;270(11):6420
AUTHOR: Muchowski P J; Zhang L; Chang E R; Soule H R; Plow E F; Moyle M
CORPORATE SOURCE: Corvas International, Inc., San Diego, California 92121.
CONTRACT NUMBER: HL-38292 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Oct 21) 269 (42) 26419-23.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411

ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19960129
Entered Medline: 19941122

AB Neutrophil **inhibitory** factor (NIF) is a **hookworm** -derived glycoprotein ligand of the **integrin** CD11b/CD18 that **inhibits** human neutrophil function (Moyle, M., Foster, D. L., McGrath, D. E., Brown, S. M., Laroche, Y., De Meutter, J., Stanssens, P., Bogowitz, C. A., Fried, V. A., Ely, J. A., Soule, H. R., and Vlasuk, G. P. (1994) J. Biol. Chem. 269, 1008-10015). Here, we present evidence that **recombinant** NIF (rNIF) associates with the approximately 200-amino acid residue I domain of CD11b/CD18 and that this interaction is essential for **inhibition** of neutrophil function by NIF. First, radiolabeled rNIF binds to a **recombinant** glutathione S-transferase fusion protein that contains the CD11b I domain. This high affinity interaction has a partial dependence on divalent cations. The association of rNIF with the CD11b I domain is specific because 125I-rNIF does not bind either a glutathione S-transferase fusion protein that contains the I domain of the **integrin** CD11a/CD18 or **recombinant** glutathione S-transferase without the I domain. Second, the CD11b I domain fusion protein effectively competes with CD11b/CD18 on human neutrophils for 125I-rNIF binding. Third, the CD11b I domain fusion protein blocks the **inhibition** of certain neutrophil functions by rNIF, including adhesion of neutrophils to human endothelial cell monolayers and adhesion-dependent release of hydrogen peroxide from neutrophils. Specificity is demonstrated by the inability of the CD11a I domain fusion protein to block either rNIF binding to neutrophils or rNIF activity. Fourth, rNIF blocks the interaction between neutrophils and fibrinogen, a CD11b/CD18 ligand that is also thought to bind the I domain of CD11b. In contrast, rNIF does not appear to block the binding of factor X to CD11b/CD18 on neutrophils. These results suggest that CD11b/CD18 has multiple distinct binding sites for its cognate ligands, including, but not limited to, the I domain. NIF interferes with the binding of a subset of these CD11b/CD18 ligands in a highly selective manner.

L25 ANSWER 56 OF 67 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 94193581 MEDLINE
DOCUMENT NUMBER: 94193581 PubMed ID: 7908286
TITLE: A **hookworm** glycoprotein that **inhibits** neutrophil function is a ligand of the **integrin** CD11b/CD18.
AUTHOR: Moyle M; Foster D L; McGrath D E; Brown S M; Laroche Y; De Meutter J; Stanssens P; Bogowitz C A; Fried V A; Ely J A; +
CORPORATE SOURCE: Corvas International Inc., San Diego, California 92121.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Apr 1) 269 (13) 10008-15.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L27427
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 19940511
Last Updated on STN: 19960129
Entered Medline: 19940505

AB The chronic survival of many endoparasites is dependent on the ability of these organisms to escape the host immune response. Identification of the molecular mechanisms by which these organisms evade this response may

Search completed by David Schreiber 308-4292

[redacted]

yield novel approaches in the development of anti-inflammatory agents. We describe here the discovery and characterization of a novel 41-kilodalton glycoprotein from the canine hookwork (**Ancylostoma** caninum) that potently **inhibits** CD11/CD18-dependent neutrophil function in vitro. Neutrophil **inhibitory** factor (NIF) blocks the adhesion of activated human neutrophils to vascular endothelial cells as well as the release of H2O2 from activated neutrophils, over a similar concentration range (IC50 10-20 nM). Studies aimed at determining the nature of the NIF binding site on neutrophils revealed selective, high affinity binding of this protein to the **integrin** CD11b/CD18. A cDNA encoding NIF was isolated from a canine **hookworm** cDNA library. NIF comprises a mature polypeptide of 257 amino acids, preceded by a 17-amino acid leader. The mature protein has 10 cysteines and has seven potential N-linked glycosylation sites. NIF has no significant sequence **homologies** to any previously reported protein. As such, NIF represents a prototype of a novel class of leukocyte function **inhibitors**.

L25 ANSWER 57 OF 67 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 95105249 MEDLINE
DOCUMENT NUMBER: 95105249 PubMed ID: 7528750
TITLE: The A-domain of beta 2 **integrin** CR3 (CD11b/CD18) is a receptor for the **hookworm**-derived neutrophil adhesion **inhibitor** NIF.
AUTHOR: Rieu P; Ueda T; Haruta I; Sharma C P; Arnaout M A
CORPORATE SOURCE: Department of Medicine, Massachusetts General Hospital, Charlestown 02129.
CONTRACT NUMBER: AI-28465 (NIAID)
DK-48549 (NIDDK)
SOURCE: JOURNAL OF CELL BIOLOGY, (1994 Dec) 127 (6 Pt 2) 2081-91.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950215
Last Updated on STN: 19960129
Entered Medline: 19950202

AB The A-domain is a approximately 200-amino acid peptide present within structurally diverse proadhesive proteins including seven **integrins**. A **recombinant** form of the A-domain of beta 2 **integrins** CR3 and LFA-1 has been recently shown to bind divalent cations and to contain binding sites for protein ligands that play essential roles in leukocyte trafficking to inflammatory sites, phagocytosis and target cell killing. In this report we demonstrate that the neutrophil adhesion **inhibitor**, NIF produced by the **hookworm** Ancyclostoma caninium is a selective CD11b A-domain binding protein. NIF bound directly, specifically and with high affinity (Kd of approximately 1 nM) to **recombinant** CD11b A-domain (r11bA). The binding reaction was characterized by rapid association and very slow dissociation, and was blocked by an anti-r11bA monoclonal antibody. No binding was observed to rCD11aA. The NIF-r11bA interaction required divalent cations, and was absent when the **mutant** r11bA D140GS/AGA (that lacks divalent cation binding capacity) was used. The NIF binding site in r11bA was mapped to four short peptides, one of which being an iC3b binding site. The interaction of NIF with CR3 in intact cells followed similar binding kinetics to those with r11bA, and occurred with similar affinity in resting and activated human neutrophils,

Search completed by David Schreiber 308-4292

suggesting that the NIF epitope is activation independent. Binding of NIF to CR3 blocked its ability to bind to its ligands iC3b, fibrinogen, and CD54, and **inhibited** the ability of human neutrophils to ingest serum opsonized particles. NIF thus represents the first example of a disintegrin that targets the **integrin** A-domain, and is likely to be used by the **hookworm** to evade the host's inflammatory response. The unique structure of NIF, which lacks a disintegrin motif, emphasizes basic structural differences in antagonists targeting A+ and A- **integrins**, that should be valuable in drug design efforts aimed at generating novel therapeutics. Identification of the region in NIF mediating A-domain binding should also be useful in this regard, and may, as in the case of disintegrins, unravel a new structural motif with cellular counterparts mediating important physiologic functions.

L25 ANSWER 58 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 19

ACCESSION NUMBER: 1995:390459 HCAPLUS
DOCUMENT NUMBER: 123:7438
TITLE: Brugia malayi: The diagnostic potential of **recombinant** excretory/secretory antigens
AUTHOR(S): Kumari, Suman; Lillibridge, C. David; Bakeer, Mona; Lowrie, Robert C. Jr.; Jayaraman, Kunthala; Philipp, Mario T.
CORPORATE SOURCE: Tulane Regional Primate Research Center, Tulane University Medical Center, Covington, LA, USA
SOURCE: Experimental Parasitology (1994), 79(4), 489-505
CODEN: EXPAAA; ISSN: 0014-4894
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The diagnostic potential of **recombinant** E/S antigens of the lymphatic filaria Brugia malayi was investigated by Western blot. A cDNA expression library was constructed using B. malayi male adult worm mRNA, and E/S **recombinants** were identified with a rabbit antiserum raised against E/S products collected in vitro from B. malayi male and female adult worms. Two of these **recombinants**, Bm12 and Bm14L, were studied after subcloning the cDNA inserts in an Escherichia coli plasmid expression and purifn. vector, obtaining the inserts' nucleotide sequence, and purifying the expressed proteins. By homol. of their deduced amino acid sequence with that of previously identified proteins, Bm12 was identified as the B. malayi gp 15/400 antigen, and Bm14 as a member of the hsp90 family of heat shock proteins. The antigenic cross-reactivity of the purified **recombinant** proteins was assessed with 28 serum samples from patients infected with Ascaris, Trichuris, or **hookworm**, and also with a few samples from patients with onchocerciasis and loiasis. For Bm12, the specificity for all of the intestinal helminthiasis together was 75%. Bm14L, on the other hand, cross-reacted with all of the ascariasis serum samples with which it was tested. Presence of antibodies cross-reactive with B. malayi was confirmed in all of these serum samples by examg. their antibody reactivity with Western blots of exts. of whole B. malayi adult worms. A semiquant. (+ or -) assessment of the sensitivity of Bm12 for antibody detection was performed using 6 serum samples from patients with chronic filariasis and 24 samples from patients with microfilaremia. All of these serum samples contained anti-Bm12 antibody (sensitivity of 100%). Finally, the ability of Bm12 to detect antibody before the onset of patency was established with a longitudinal collection of serum samples obtained from 2 African green vervets (Cercopithecus aethiops) and 3 rhesus macaques (Macaca mulatta), all of which were infected with B. malayi. Anti-Bm12 antibodies were detectable in all animals between 4 and 11 wk before patency.

Search completed by David Schreiber 308-4292

L25 ANSWER 59 OF 67 MEDLINE on STN
ACCESSION NUMBER: 95159088 MEDLINE
DOCUMENT NUMBER: 95159088 PubMed ID: 7855801
TITLE: Inventory of coagulation **inhibitors** from animals feeding on blood. A report prepared on behalf of the Scientific and Standardization Committee's Registry of Exogenous Hemostatic Factors.
AUTHOR: Markwardt F
CORPORATE SOURCE: Medical Academy Erfurt, Department of Pharmacology, Germany.
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1994 Sep) 72 (3) 477-80. Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950314

L25 ANSWER 60 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:183017 HCAPLUS
DOCUMENT NUMBER: 120:183017
TITLE: Native and **recombinant** neutrophil **inhibitory** factors, and their use in treatment of inflammatory response
INVENTOR(S): Moyle, Matthew; Foster, David Lee; Vlasuk, George Phillip
PATENT ASSIGNEE(S): Corvas International, Inc., USA
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9323063	A1	19931125	WO 1993-US4502	19930511
W: AU, CA, FI, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9342464	A1	19931213	AU 1993-42464	19930511
AU 687737	B2	19980305		
JP 07508177	T2	19950914	JP 1993-503717	19930511
EP 731709	A1	19960918	EP 1993-911273	19930511
EP 731709	B1	20011024		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 207498	E	20011115	AT 1993-911273	19930511
ES 2168095	T3	20020601	ES 1993-911273	19930511
US 5708141	A	19980113	US 1994-249041	19940524
NZ 299623	A	20001124	NZ 1996-299623	19961023
NZ 505450	A	20020201	NZ 1999-505450	19990113
PRIORITY APPLN. INFO.:			US 1992-881721 A	19920511
			US 1992-996972 A	19921224
			WO 1993-US4502 A	19930511

AB Compns. enriched for neutrophil **inhibitory** factor (NIF) which **inhibit** neutrophil activity including adhesion to vascular

Search completed by David Schreiber 308-4292

endothelial cells are provided. Such compns. may comprise a glycoprotein isolated from nematodes. These compns. are useful in the therapy of conditions which involve abnormal or undesired inflammatory responses. Native NIF was. prepd. from a lysate of Toxocara canis and characterized. Cloning and sequencing of NIF is described, as is expression of **recombinant** NIF in COS7 cells and in Pichia pastoris. Data are presented which strongly suggest that Mac-1 **integrin** is a major receptor for NIF on leukocytes. **Recombinant** NIF **inhibited** neutrophil-mediated inflammation in vivo (rat ear inflammation assay).

L25 ANSWER 61 OF 67 MEDLINE on STN
ACCESSION NUMBER: 86098119 MEDLINE
DOCUMENT NUMBER: 86098119 PubMed ID: 4082263
TITLE: Resistance of dogs to reinfection with **Ancylostoma** ceylanicum following anthelmintic therapy.
AUTHOR: Carroll S M; Grove D I
SOURCE: TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, (1985) 79 (4) 519-23.
Journal code: 7506129. ISSN: 0035-9203.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860220

AB A model of human **hookworm** infection has been developed which shows that dogs with chronic **hookworm** infection are considerably resistant to reinfection one month after the termination of the primary infection with anthelmintics. Challenge and control dogs were infected with 1,800 larvae and the infection was followed for six weeks. When compared with control dogs, faecal egg excretion and intestinal adult worm burdens in challenge dogs were reduced by 85% and 77%, respectively. Infection had no significant effect on haemoglobin concentrations, total white cell counts, **platelet** levels or spontaneous and phytohaemagglutinin-induced lymphocyte transformations in both control and previously infected dogs. Both groups of dogs developed an eosinophilia and lymphocytes responded transiently to stimulation with both larval and adult worm antigens, although there were no significant differences between the two groups of animals. Specific IgM antibodies were transient in both groups of animals following infection. Specific IgG antibodies were present at high levels before infection in challenge dogs when compared with control dogs, and fell transiently after challenge; three weeks after infection, IgG antibodies appeared in the control animals and titres continued to rise during the period of observation. Challenge dogs also developed specific IgA antibodies three weeks after infection, and these remained at high levels, but these antibodies were not detected in control dogs. Thus, dogs infected with this strain of the **hookworm**, **Ancylostoma** ceylanicum, which has been shown to infect man, develop functional protective immunity. These findings improve prospects for **vaccine** development.

L25 ANSWER 62 OF 67 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 86082218 MEDLINE
DOCUMENT NUMBER: 86082218 PubMed ID: 4076382
TITLE: **Ancylostoma** ceylanicum: **immunization** with soluble worm extract and responses to challenge

Search completed by David Schreiber 308-4292

infection of dogs.
AUTHOR: Carroll S M; Grove D I
SOURCE: EXPERIMENTAL PARASITOLOGY, (1985 Dec) 60 (3) 263-9.
Journal code: 0370713. ISSN: 0014-4894.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198601
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860129

AB When dogs were **immunized** with soluble extract of adult **Ancylostoma** ceylanicum antigen, they were partially resistant to challenge infection in this model of human **hookworm** infection. Two **immunizing** doses, each of 1 mg protein suspended in Freund's complete adjuvant, were administered to one group of animals 1 and 3 weeks prior to infection with 5000 larvae. When compared with control dogs given the same infective dose, fecal egg excretion and intestinal adult worm burden in the **immunized** animals were reduced by 59 and 74%, respectively. Infection had no significant effect on hemoglobin concentrations, mean red cell volumes, total white cell counts, **platelet** levels, or spontaneous and phytohemagglutinin-induced lymphocyte transformations in both control and **immunized** animals. Both groups developed an eosinophilia, and lymphocytes from the **immunized** dogs responded transiently to stimulation with both larval and adult worm antigens. Specific IgM antibodies were transitory in both groups of dogs following infection. IgG antibodies developed significantly 2 weeks after infection in the **immunized** group; however, they did not appear until 4 weeks after infection in the control group. Both groups developed IgA antibodies 1 week after infection. They were maintained in the control dogs, in contrast to the levels in **immunized** animals which subsided rapidly 4 weeks after infection. Therefore, when animals are injected with soluble adult worm antigen prior to infection, specific protective immunity is acquired.

L25 ANSWER 63 OF 67 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 84250806 MEDLINE
DOCUMENT NUMBER: 84250806 PubMed ID: 6740554
TITLE: The anticoagulant effects of the **hookworm**, **ancylostoma** ceylanicum: observations on human and dog blood in vitro and infected dogs in vivo.
AUTHOR: Carroll S M; Howse D J; Grove D I
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1984 Apr 30) 51 (2) 222-7.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198408
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19840813

AB Extracts of adult **Ancylostoma** ceylanicum prolonged the prothrombin time (PT) and partial thromboplastin time with kaolin (PPTK) of both human and dog plasmas in vitro. Excretory/secretory (E/S) products of these worms had similar effects while larval extract prolonged the PTTK only. Thus, the anticoagulant activities of this parasite are dependent upon the stage of the worm's life cycle. Collagen- and

ADP-induced **platelet** aggregation were **inhibited** by adult and larval extracts. When the peripheral blood and bleeding times of dogs with varying worm burdens were examined, the only abnormality was shortening of the PTTK in the most heavily infected animals. Homogenates of dog small bowel subjacent to adult hookworms prolonged the PT of dog plasma and electron microscopical examination of this tissue revealed aggregation of **platelets** in blood venules without fibrin deposition. Thus, this study provides evidence that the anticoagulant properties of hookworms may have biological significance in infected animals.

L25 ANSWER 64 OF 67 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 83171204 MEDLINE
DOCUMENT NUMBER: 83171204 PubMed ID: 6682241
TITLE: Transient non-thrombocytopenic purpura in **hookworm** infestation.
AUTHOR: Kueh Y K; Chan L; Lim B C; Wong H B
SOURCE: SCANDINAVIAN JOURNAL OF HAEMATOLOGY, (1983 Feb) 30 (2) 174-6.
Journal code: 0404507. ISSN: 0036-553X.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198305
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830505

AB The transient purpura in 3 young men with marked eosinophilia and **hookworm** infestation was found to be caused by a qualitative **platelet** defect which manifested as a failure of **platelets** to aggregate with collagen and an absence of the secondary phase aggregation with **epinephrine**. These aggregation abnormalities could not be normalized with normal plasma, nor did patient plasma **inhibit** normal **platelets**, implying that the dysfunction was not caused by an abnormality in the plasma but was an intrinsic **platelet** defect. Arachidonic acid induced enhanced aggregation and a mutual correction of the absent secondary **epinephrine** -induced aggregation was observed when patient and aspirin-treated **platelets** were mixed together, suggesting that the defect was unlikely to be related to the **platelet** prostaglandin synthesis pathway. We propose that the acquired **platelet** dysfunction was caused by impaired **ADP** release due possibly to a transient **platelet** storage pool abnormality.

L25 ANSWER 65 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1984:17267 BIOSIS
DOCUMENT NUMBER: BR26:17267
TITLE: PARASITE DEPENDENT MODULATION OF ACUTE INFLAMMATION REVIEW.
AUTHOR(S): LEID R W
CORPORATE SOURCE: DEP. VET. MICROBIOL. PATHOL., WASH. STATE UNIV., PULLMAN, WA 99164.
SOURCE: CONFERENCE ON IMMUNOPARASITOLOGY, LINCOLN, NEB., USA, JUNE 17-19, 1981. VET PARASITOL, (1982) 10 (2-3), 155-170.
CODEN: VPARDI. ISSN: 0304-4017.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L25 ANSWER 66 OF 67 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 23

Search completed by David Schreiber 308-4292

Kam 09/937,555

ACCESSION NUMBER: 1971:137054 HCAPLUS
DOCUMENT NUMBER: 74:137054
TITLE: Anticoagulant activity of dog **hookworm**
AUTHOR(S): Spellman, G. G., Jr.; Nossel, Hymie L.
CORPORATE SOURCE: Coll. Physicians Surg., Columbia Univ., New York, NY, USA
SOURCE: American Journal of Physiology (1971), 220(4), 922-7
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The dog **hookworm** (**Ancylostoma** caninum) exerted a potent anticoagulant effect and studies were made on the mechanism of this effect. Increasing concns. of **hookworm** ext. progressively prolonged the prothrombin time and partial thromboplastin time to an approx. equiv. extent but caused much less prolongation of the Russell's viper venom (RVV) clotting time. The anticoagulant action was not heparinlike in that there was no effect on the **thrombin** time. The anticoagulant **inhibited** activated factor X as indicated by anticoagulant effect when activated factor X was added to factor X-deficient plasma or to purified prothrombin. The **hookworm** ext. **inhibited** Russell's viper venom-activated factor X (from which the RVV was removed) to a lesser extent than it **inhibited** thromboplastin-factor VII-activated factor X (from which the thromboplastin was removed). The activated factor X mol. may vary depending on the mode of activation. **Hookworm** ext. also **inhibited** collagen and **ADP**-induced **platelet** aggregation and inactivated **ADP** via a time consuming temp.-dependent reaction.

L25 ANSWER 67 OF 67 MEDLINE on STN
ACCESSION NUMBER: 70085313 MEDLINE
DOCUMENT NUMBER: 70085313 PubMed ID: 5460786
TITLE: Immune reactions to Nippostrongylus brasiliensis in the rat. I. Characteristics of primary and secondary immune response in vivo.
AUTHOR: Keller R
SOURCE: INTERNATIONAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY, (1970) 37 (2) 197-215.
Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197003
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19970203
Entered Medline: 19700302

Search completed by David Schreiber 308-4292